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(54) Title: SELECTIVE S1P1/EDG1 RECEPTOR AGONISTS

(57) Abstract: The present invention encompasses a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the S1P1/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor, said compound administered in an amount effective for treating said immunoregulatory abnormality. Pharmaceutical compositions are included. The invention also encompasses a method of identifying candidate compounds that are agonists of the S1P1/Edg1 receptor and which possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor. The invention further encompasses a method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the S1P1/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor.

TITLE OF THE INVENTION
SELECTIVE S1P1/EDG1 RECEPTOR AGONISTS

BACKGROUND OF THE INVENTION

The present invention is related to compounds that are selective $S1P_1$/Edg1 receptor agonists and thus have immunosuppressive activities by producing lymphocyte sequestration in secondary lymphoid tissues. The invention is also directed to pharmaceutical compositions containing such compounds and methods of treatment or prevention.

Immunosuppressive agents have been shown to be useful in a wide variety of autoimmune and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis and other disorders such as Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy, atopic dermatitis and asthma. They have also proved useful as part of chemotherapeutic regimens for the treatment of cancers, lymphomas and leukemias.

Although the underlying pathogenesis of each of these conditions may be quite different, they have in common the appearance of a variety of autoantibodies and/or self-reactive lymphocytes. Such self-reactivity may be due, in part, to a loss of the homeostatic controls under which the normal immune system operates. Similarly, following a bone-marrow or an organ transplantation, the host lymphocytes recognize the foreign tissue antigens and begin to produce both cellular and humoral responses including antibodies, cytokines and cytotoxic lymphocytes which lead to graft rejection.

One end result of an autoimmune or a rejection process is tissue destruction caused by inflammatory cells and the mediators they release. Anti-inflammatory agents such as NSAIDs act principally by blocking the effect or secretion of these mediators but do nothing to modify the immunologic basis of the disease. On the other hand, cytotoxic agents, such as cyclophosphamide, act in such a nonspecific fashion that both the normal and autoimmune responses are shut off. Indeed, patients treated with such nonspecific immunosuppressive agents are as likely to succumb to infection as they are to their autoimmune disease.

Cyclosporin A is a drug used to prevent rejection of transplanted organs. FK-506 is another drug approved for the prevention of transplant organ rejection, and in particular, liver transplantation. Cyclosporin A and FK-506 act by inhibiting the body's immune system from mobilizing its vast arsenal of natural protecting agents to reject the transplant's foreign protein. Cyclosporin A was approved for the treatment of severe psoriasis and has been approved by European regulatory agencies for the treatment of atopic dermatitis.

Though they are effective in delaying or suppressing transplant rejection, Cyclosporin A and FK-506 are known to cause several undesirable side effects including nephrotoxicity, neurotoxicity, and gastrointestinal discomfort. Therefore, an immunosuppressant without these side effects still remains to be developed and would be highly desirable.

The immunosuppressive compound FTY720 is a lymphocyte sequestration agent currently in clinical trials. FTY720 is metabolized in mammals to a compound that is a potent agonist of sphingosine 1-phosphate receptors. Agonism of sphingosine 1-phosphate receptors induces the sequestration of lymphocytes (T-cells and B-cells) in lymph nodes and Peyer's patches without lymphodepletion. Such immunosuppression is desirable to prevent rejection after organ transplantation and in the treatment of autoimmune disorders.

Sphingosine 1-phosphate is a bioactive sphingolipid metabolite that is secreted by hematopoietic cells and stored and released from activated platelets. Yatomi, Y., T. Ohmori, G. Rile, F. Kazama, H. Okamoto, T. Sano, K. Satoh, S. Kume, G. Tigyi, Y. Igarashi, and Y. Ozaki. 2000. *Blood.* 96:3431-8. It acts as an agonist on a family of G protein-coupled receptors to regulate cell proliferation, differentiation, survival, and motility. Fukushima, N., I. Ishii, J.J.A. Contos, J.A. Weiner, and J. Chun. 2001. Lysophospholipid receptors. Annu. Rev. Pharmacol. Toxicol. 41:507-34; Hla, T., M.-J. Lee, N. Ancellin, J.H. Paik, and M.J. Kluk. 2001. Lysophospholipids - Receptor revelations. *Science.* 294:1875-1878; Spiegel, S., and S. Milstien. 2000. Functions of a new family of sphingosine-1-phosphate receptors. *Biochim. Biophys. Acta.* 1484:107-16; Pyne, S., and N. Pyne. 2000. Sphingosine 1-phosphate signalling via the endothelial differentiation gene family of G-protein coupled receptors. *Pharm. & Therapeutics.* 88:115-131. Five sphingosine 1-phosphate receptors have been identified ($S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, and $S1P_5$, also

known as endothelial differentiation genes Edg1, Edg5, Edg3, Edg6, Edg8), that have widespread cellular and tissue distribution and are well conserved in human and rodent species (see Table). Binding to S1P receptors elicits signal transduction through Gq-, Gi/o, G12-, G13-, and Rho-dependent pathways. Ligand-induced activation of $S1P_1$ and $S1P_3$ has been shown to promote angiogenesis, chemotaxis, and adherens junction assembly through Rac- and Rho-, *see* Lee, M.-J., S. Thangada, K.P. Claffey, N. Ancellin, C.H. Liu, M. Kluk, M. Volpi, R.I. Sha'afi, and T. Hla. 1999. *Cell.* 99:301-12, whereas agonism of $S1P_2$ promotes neurite retraction, *see* Van Brocklyn, J.R., Z. Tu, L.C. Edsall, R.R. Schmidt, and S. Spiegel. 1999. *J. Biol. Chem.* 274:4626-4632, and inhibits chemotaxis by blocking Rac activation, *see* Okamoto, H., N. Takuwa, T. Yokomizo, N. Sugimoto, S. Sakurada, H. Shigematsu, and Y. Takuwa. 2000. *Mol. Cell. Biol.* 20:9247-9261. S1P4 is localized to hematopoietic cells and tissues, *see* Graeler, M.H., G. Bernhardt, and M. Lipp. 1999. *Curr. Top. Microbiol. Immunol.* 246:131-6, whereas $S1P_5$ is primarily a neuronal receptor with some expression in lymphoid tissue, *see* Im, D.S., C.E. Heise, N. Ancellin, B.F. O'Dowd, G.J. Shei, R.P. Heavens, M.R. Rigby, T. Hla, S. Mandala, G. McAllister, S.R. George, and K.R. Lynch. 2000. *J. Biol. Chem.* 275:14281-6. Administration of sphingosine 1-phosphate to animals induces systemic sequestration of peripheral blood lymphocytes into secondary lymphoid organs, stimulates FGF-mediated blood vessel growth and differentiation, *see* Lee, et al., supra, but also has cardiovascular effects that limit the utility of sphingosine 1-phosphate as a therapeutic agent, *see* Sugiyama, A., N.N. Aye, Y. Yatomi, Y. Ozaki, and K. Hashimoto. 2000. *Jpn. J. Pharmacol.* 82:338-342. The reduced heart rate and blood pressure measured with sphingosine 1-phosphate is associated with its non-selective, potent agonist activity on all S1P receptors.

The present invention is directed towards compounds which are selective agonists of the $S1P_1$/Edg1 receptor while having the specified window of selectivity as agonists of, or alternately antagonists or inverse agonists of the $S1P_3$/Edg3 receptor. An $S1P_1$/Edg1 receptor selective agonist has advantages over current therapies and extends the therapeutic window of lymphocytes sequestration agents, allowing better tolerability with higher dosing and thus improving efficacy as monotherapy. Receptor agonists selective for $S1P_1$/Edg1 over $S1P_3$/Edg3 having enhanced cardiovascular tolerability in rats are exemplified.

While the main use for immunosuppressants is in treating bone marrow, organ and transplant rejection, other uses for such compounds include the treatment of arthritis, in particular, rheumatoid arthritis, insulin and non-insulin dependent diabetes, multiple sclerosis, psoriasis, inflammatory bowel disease, Crohn's disease, lupus erythematosis and the like.

Thus, the present invention is focused on providing immunosuppressant compounds that are safer and more effective than prior compounds. These and other objects will be apparent to those of ordinary skill in the art from the description contained herein.

Summary of S1P receptors

Name	Synonyms	Coupled G proteins	mRNA expression
$S1P_1$	Edg1, LP_{B1}	$G_{i/o}$	Widely distributed, endothelial cells
$S1P_2$	Edg5, LP_{B2}, AGR16, H218	$G_{i/o}$, G_q, $G_{12/13}$	Widely distributed, vascular smooth muscle cells
$S1P_3$	Edg3, LP_{B3}	$G_{i/o}$, G_q, $G_{12/13}$	Widely distributed, endothelial cells
$S1P_4$	Edg6, LP_{C1}	$G_{i/o}$	Lymphoid tissues, lymphocytic cell lines
$S1P_5$	Edg8, LP_{B4}, NRG1	$G_{i/o}$	Brain, spleen

SUMMARY OF THE INVENTION

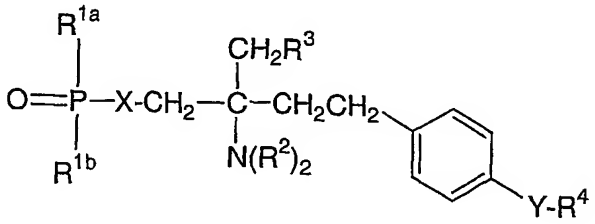
The present invention encompasses a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1

receptor over the S1PR3/Edg3 receptor, said compound administered in an amount effective for treating said immunoregulatory abnormality. Pharmaceutical compositions are included. The invention also encompasses a method of identifying candidate compounds that are agonists of the $S1P_1$/Edg1 receptor and which possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor. The invention further encompasses a method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor.

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

An embodiment of the invention encompasses the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the

S1P3/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

The invention also encompasses a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

Within this embodiment is encompassed the above method wherein the compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

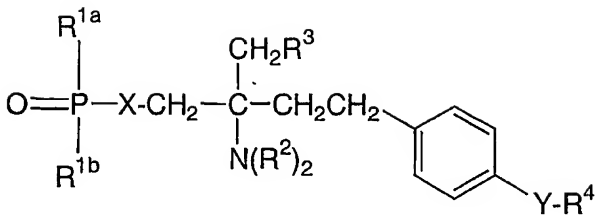
Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1PR3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1PR3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

The invention also encompasses a pharmaceutical composition comprised of a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the $S1P_1$/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl,

in combination with a pharmaceutically acceptable carrier.

The present invention also encompasses a pharmaceutical composition comprised of a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay, in combination with a pharmaceutically acceptable carrier.

For purposes of this specification, when a compound is said to be evaluated by the ^{35}S-GTPγS binding assay, this means said compound is evaluated following the procedures described herein under the heading ^{35}S-GTPγS binding assay.

The present invention is directed towards compounds which are selective agonists of the $S1P_1$/Edg1 receptor while having the specified window of selectivity as agonists of, or alternately antagonists or inverse agonists of the $S1P_3$/Edg3 receptor. The invention also encompasses compounds that are agonists of the $S1P_1$/Edg1 receptor while having the specified window of selectivity as non-modulators of the $S1P_3$/Edg3 receptor.

A further embodiment of the invention encompasses the concomitant administration of an $S1P_1$/Edg1 receptor in combination with an antagonist or inverse agonist of the $S1P_3$/Edg3 receptor, such that the combined therapy possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

The invention also encompasses the above method wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease selected from the group consisting of: systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary

cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

The invention also encompasses the above method wherein the immunoregulatory abnormality is bone marrow or organ transplant rejection or graft-versus-host disease.

The invention also encompasses the above method wherein the immunoregulatory abnormality is selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic

anemia, anerythroplasia, chronic lymphocytic leukemia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

The invention also encompasses the above method wherein the immunoregulatory abnormality is multiple sclerosis.

The invention also encompasses the above method wherein the immunoregulatory abnormality is rheumatoid arthritis.

The invention also encompasses the above method wherein the immunoregulatory abnormality is systemic lupus erythematosus.

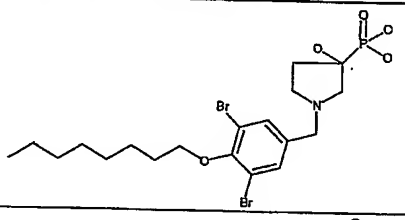
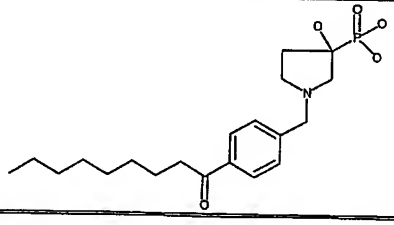
The invention also encompasses the above method wherein the immunoregulatory abnormality is psoriasis.

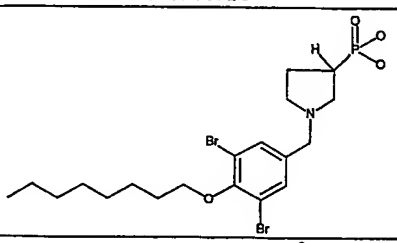
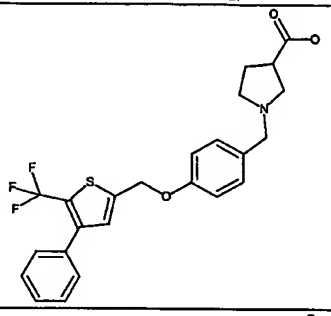
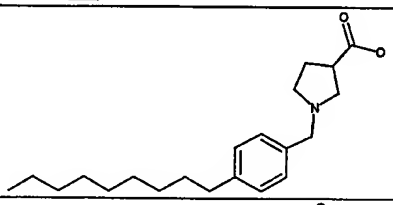
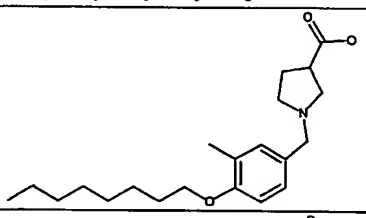
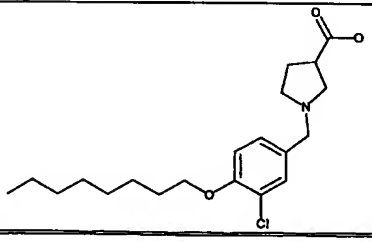
The invention also encompasses the above method wherein the immunoregulatory abnormality is rejection of transplanted organ or tissue.

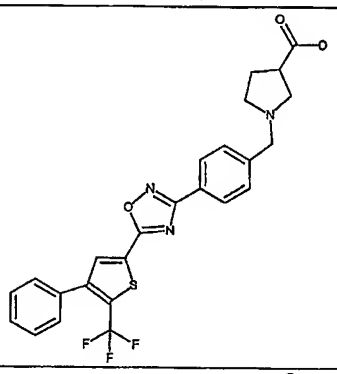
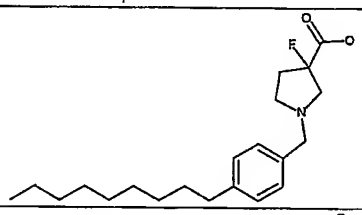
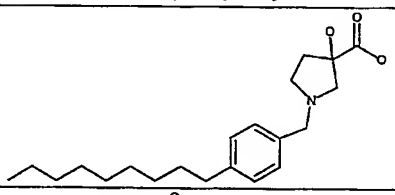
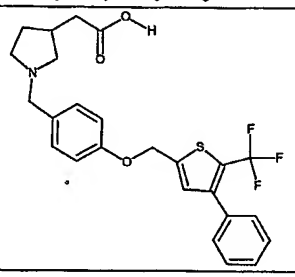
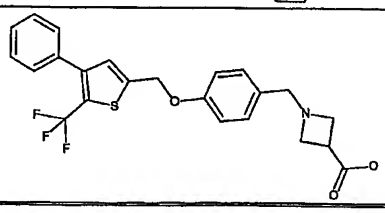
The invention also encompasses the above method wherein the immunoregulatory abnormality is inflammatory bowel disease.

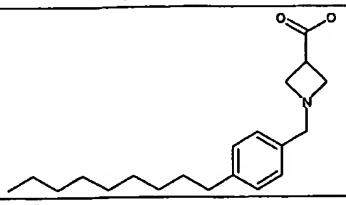
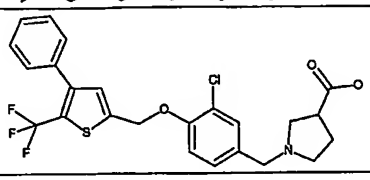
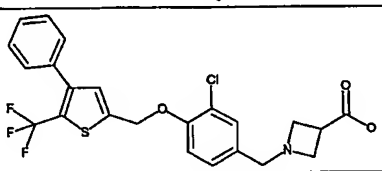
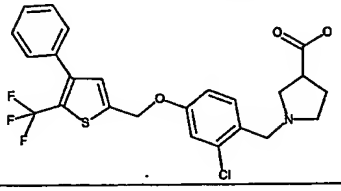
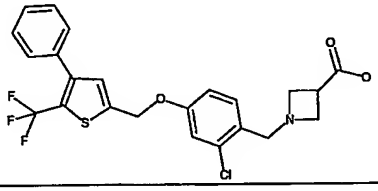
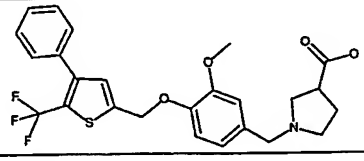
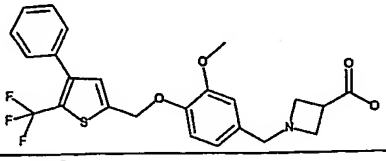
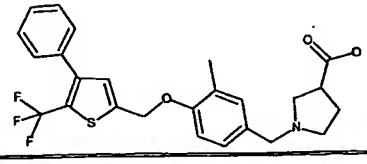
The invention also encompasses the above method wherein the immunoregulatory abnormality is a malignancy of lymphoid origin, such as acute and chronic lymphocytic leukemias and lymphomas.

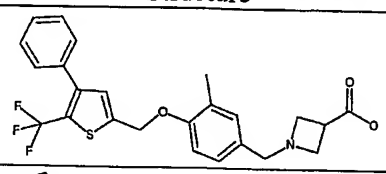
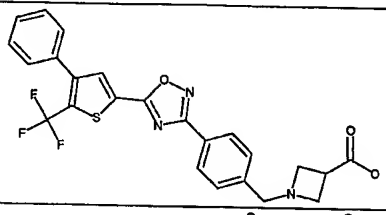
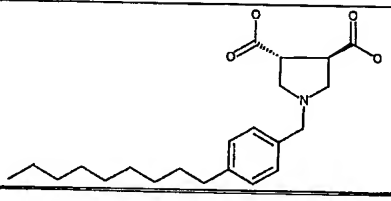
Exemplifying the invention are the following compounds, which possess a selectivity for the $S1P_1$/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and which possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay:

Example No.	Structure
VII	
VIII	

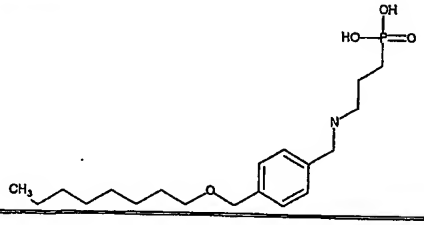
Example No.	Structure
XV + XVI	
XVIII	
XIX	
XXIII	
XXVI	

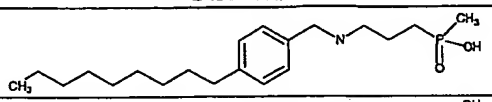
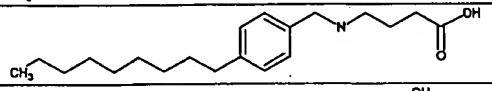
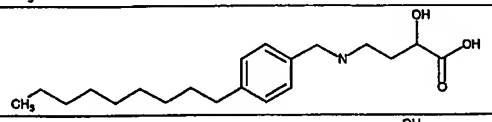
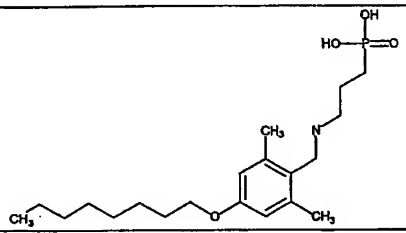
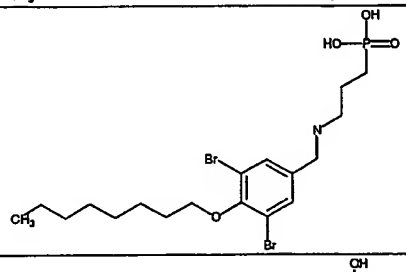
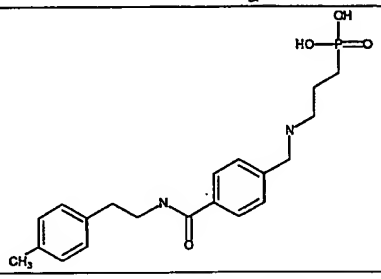
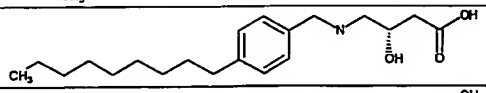
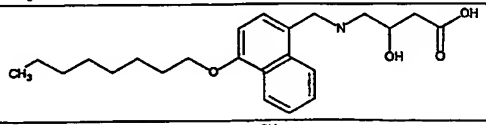
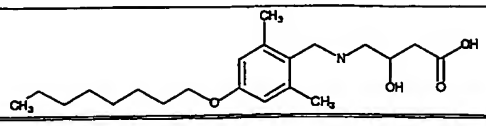
Example No.	Structure
XXVIII	
XXXV	
XXXVI	
XXXVIII	
XL	

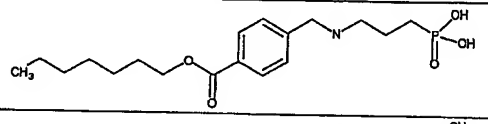
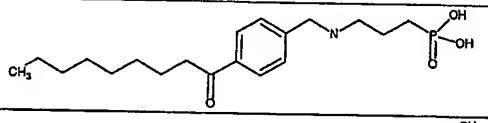
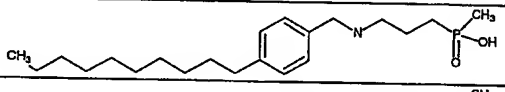
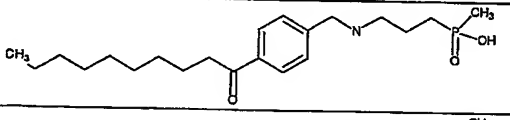
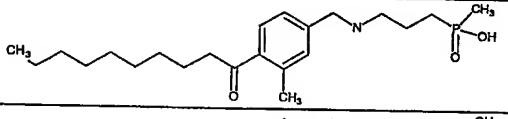
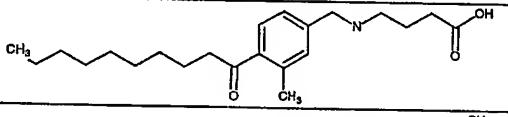
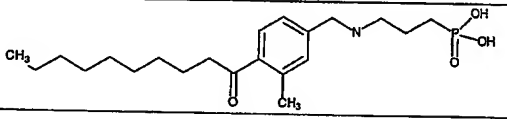
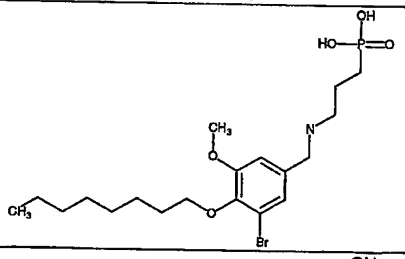
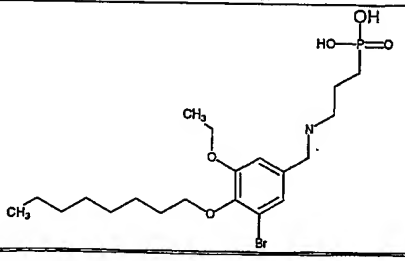
Example No.	Structure
XLI	
XLVI	
XLVII	
XLVIII	
XLIX	
L	
LI	
LII	

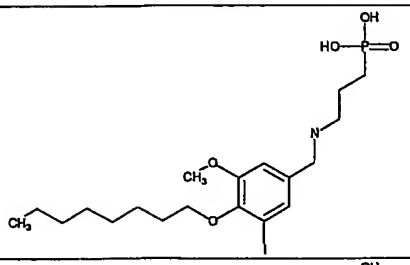
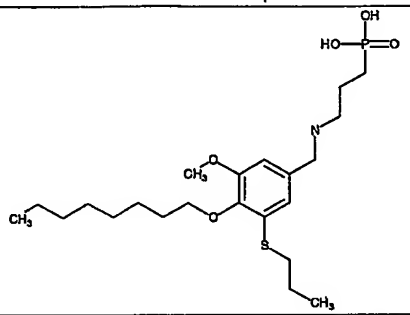
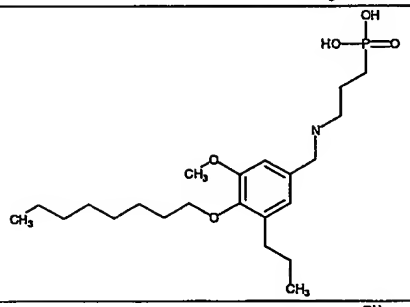
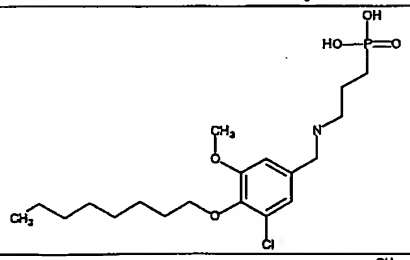
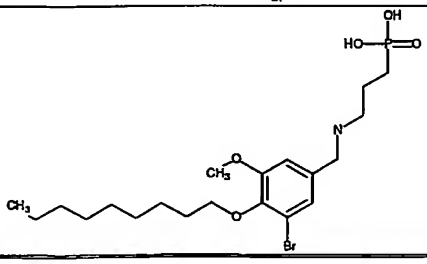
Example No.	Structure
LIII	
LIV	
LVII	

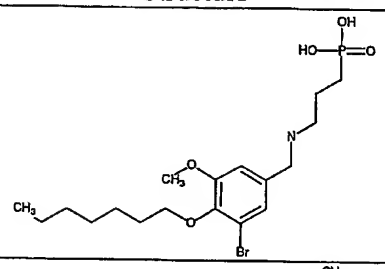
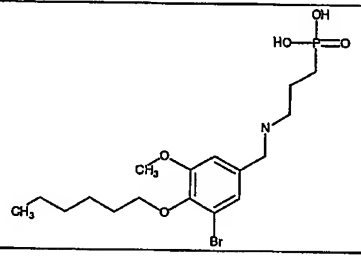
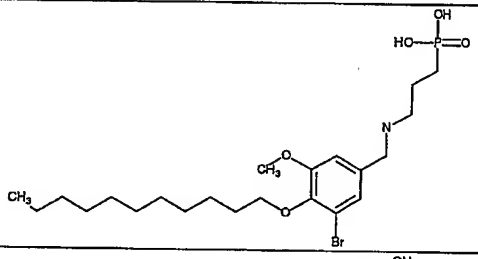
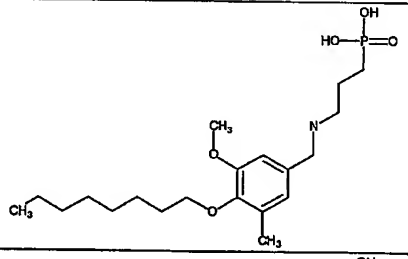
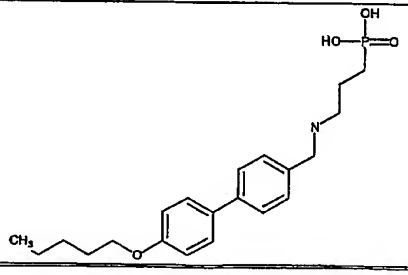
Further exemplifying the invention are the following compounds, which possess a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and which possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay:

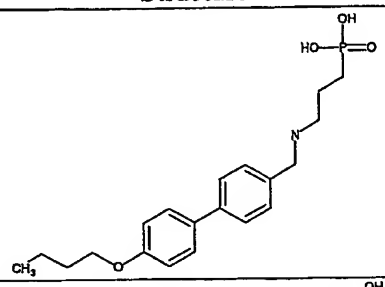
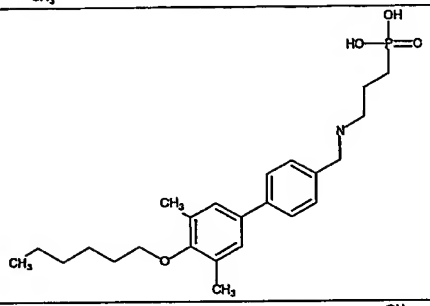
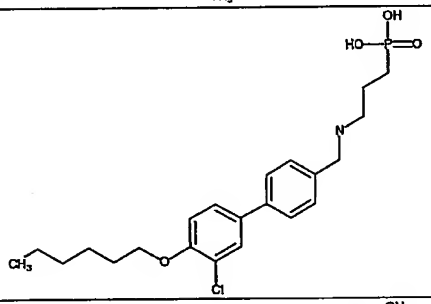
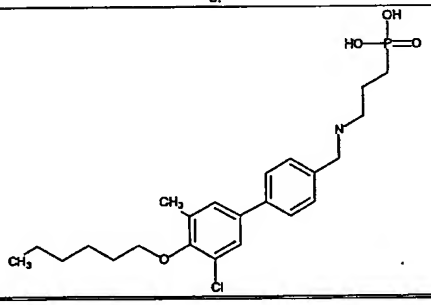
Example Number	Structure
6	

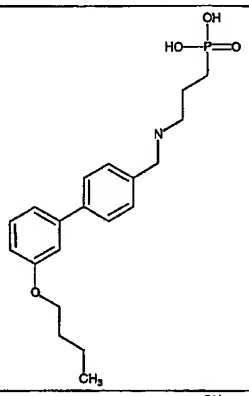
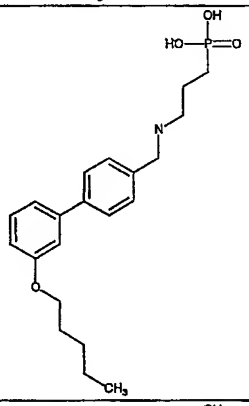
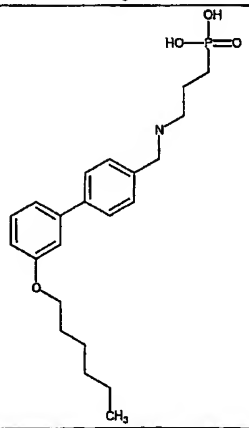
Example Number	Structure
12	
15	
16	
24	
25	
34	
41	
43	
44	

Example Number	Structure
45	
47	
48	
51	
53	
54	
55	
58	
59	

Example Number	Structure
66	
67	
68	
70	
71	

Example Number	Structure
72	
77	
78	
81	
84	

Example Number	Structure
85	
88	
89	
91	

Example Number	Structure
93	
94	
95	

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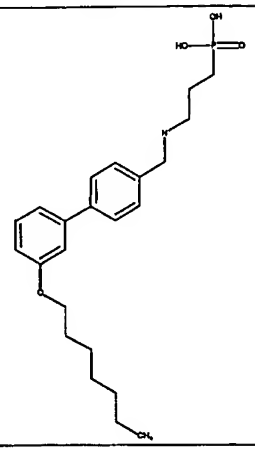
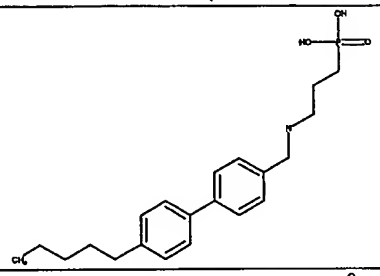
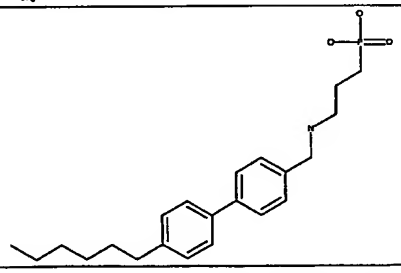
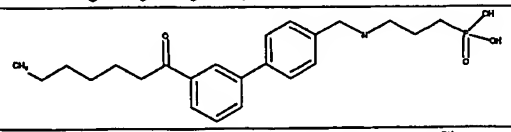
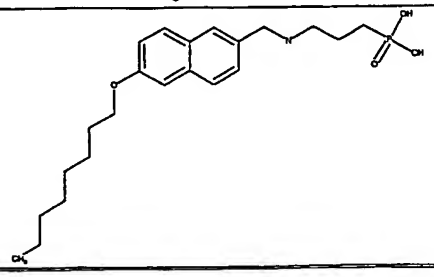
98	
99	
100	
103	
105	

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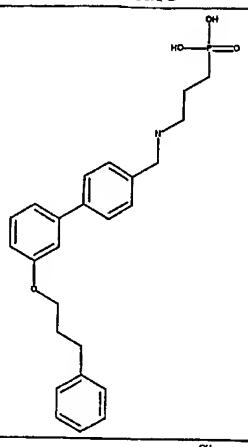
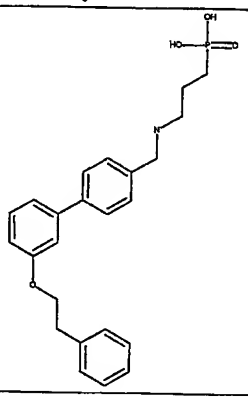
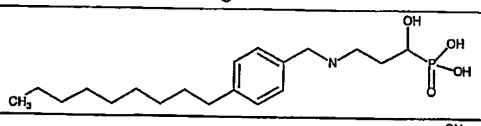
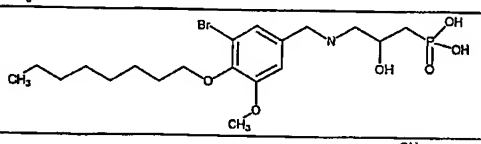
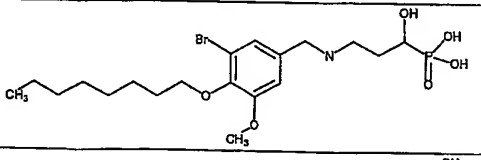
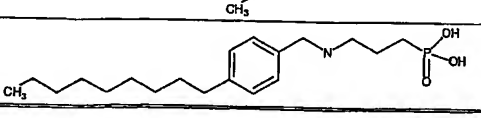
106	
107	
108	
110	
111	
112	

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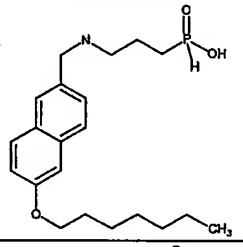
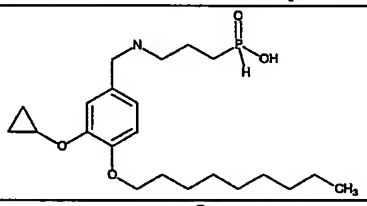
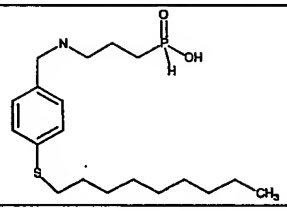
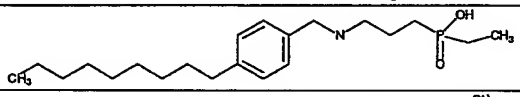
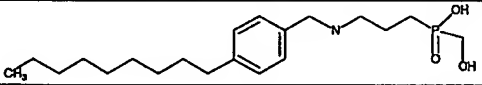
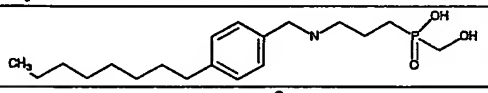
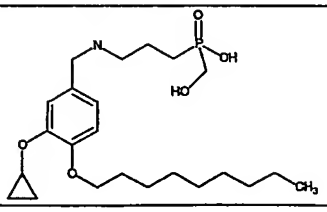
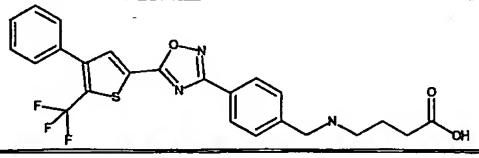
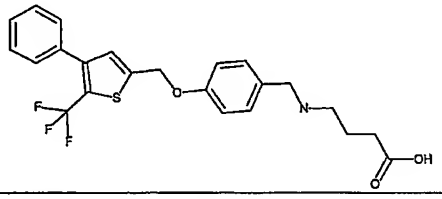
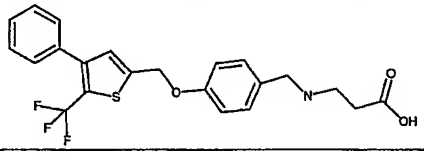
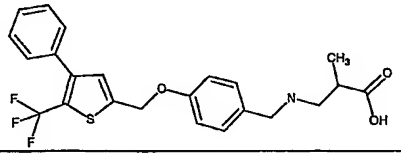
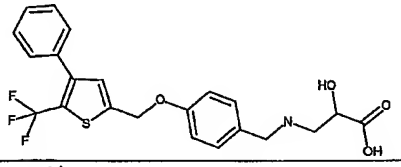
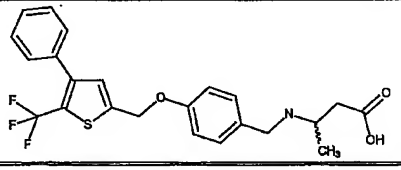
122	
123	
124	
125	
128	
134	
135	
141	

Example Number	Structure
143	
144	
145	
146	
149	

The invention is described using the following definitions unless otherwise indicated.

The term "halogen" or "halo" includes F, Cl, Br, and I.

The term "alkyl" means linear or branched structures and combinations thereof, having the indicated number of carbon atoms. Thus, for example, C_{1-6}alkyl includes methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "haloalkyl" means alkyl as defined above substituted with at least one halo group, as defined above, and being optionally substituted with halo up to the maximum number of substituable positions.

The term "hydroxyalkyl" means alkyl as defined above substituted with at least one hydroxy group, and being optionally substituted with hydroxyup to the maximum number of substituable positions.

The term "alkoxy" means alkoxy groups of a straight, branched or cyclic configuration having the indicated number of carbon atoms. C_{1-6}alkoxy, for example, includes methoxy, ethoxy, propoxy, isopropoxy, and the like.

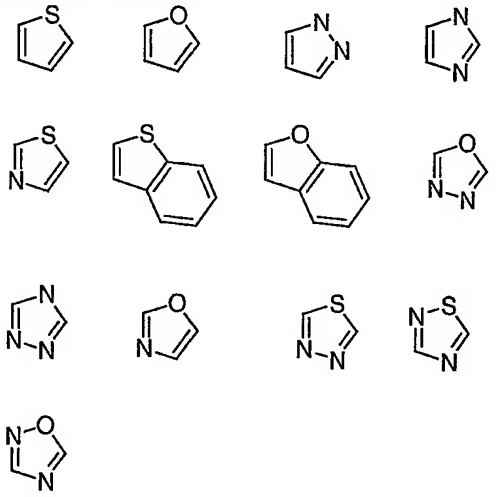
The term "alkylthio" means alkylthio groups having the indicated number of carbon atoms of a straight, branched or cyclic configuration. C_{1-6}alkylthio, for example, includes methylthio, propylthio, isopropylthio, and the like.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon-to-carbon double bond. C_{2-6}alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "alkynyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon triple bond. C_{3-6}alkynyl, for example, includes , propenyl, 1-methylethenyl, butenyl and the like.

The term "HET" is defined as a 5- to 10-membered aromatic, partially aromatic or non-aromatic mono- or bicyclic ring, containing 1-5 heteroatoms selected from O, S and N, and optionally substituted with 1-2 oxo groups. Preferably, "HET" is a 5- or 6-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N, for example, pyridine, pyrimidine, pyridazine, furan, thiophene, thiazole, oxazole, isooxazole and the like, or heterocycle is a 9- or 10-membered aromatic or partially aromatic bicyclic ring containing 1-3 heteroatoms selected from O, S, and N, for example, benzofuran, benzothiophene, indole, pyranopyrrole, benzopyran, quionoline, benzocyclohexyl, naphtyridine and the like. "HET" also includes the following: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl,

azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl. A preferred group of HET is as follows:



The term "treating" encompasses not only treating a patient to relieve the patient of the signs and symptoms of the disease or condition but also prophylactically treating an asymptomatic patient to prevent the onset or progression of the disease or condition. The term "amount effective for treating" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term also encompasses the amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

The invention described herein includes pharmaceutically acceptable salts and hydrates. Pharmaceutically acceptable salts include both the metallic

(inorganic) salts and organic salts; a list of which is given in *Remington's Pharmaceutical Sciences*, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity and solubility. As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to salts of inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts of an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate or pamoate, salicylate and stearate. Similarly pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium (especially ammonium salts with secondary amines). Preferred salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts. Also included within the scope of this invention are crystal forms, hydrates and solvates of the compounds of the present invention.

For purposes of this Specification, "pharmaceutically acceptable hydrate" means the compounds of the instant invention crystallized with one or more molecules of water to form a hydrated form.

The invention also includes the compounds falling within the present invention in the form of one or more stereoisomers, in substantially pure form or in the form of a mixture of stereoisomers. All such isomers are encompassed within the present invention.

The compounds disclosed herein are selective agonists of the $S1P_1$/Edg1 receptor while having the specified window of selectivity as agonists of, or alternately antagonists or inverse agonists of the $S1P_3$/Edg3 receptor. An Edg1 selective agonist has advantages over current therapies and extends the therapeutic window of lymphocytes sequestration agents, allowing better tolerability of higher dosing and thus improving efficacy as monotherapy. The compounds disclosed herein are useful to suppress the immune system in instances where immunosuppression is in order, such as in bone marrow, organ or transplant rejection, autoimmune and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid,

sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

More particularly, the compounds disclosed herein are useful to treat or prevent a disease or disorder selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma,

Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C_4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

Also embodied within the present invention is a method of preventing or treating resistance to transplantation or transplantation rejection of organs or tissues in a mammalian patient in need thereof, which comprises administering a therapeutically effective amount of the compounds of the present invention.

A method of suppressing the immune system in a mammalian patient in need thereof, which comprises administering to the patient an immune system suppressing amount of the compounds of the present invention is yet another embodiment.

Most particularly, the method described herein encompasses a method of treating or preventing bone marrow or organ transplant rejection which is comprised of admininstering to a mammalian patient in need of such treatment or prevention a compound of the present invention, or a pharmaceutically acceptable salt

or hydrate thereof, in an amount that is effective for treating or preventing bone marrow or organ transplant rejection.

A pharmaceutical formulation of the present invention comprises a pharmaceutically acceptable carrier and a compound disclosed herein or a pharmaceutically acceptable salt or hydrate thereof. A preferred embodiment of the formulation is one where a second immunosuppressive agent is also included. Examples of such second immunosuppressive agents are, but are not limited to azathioprine, brequinar sodium, deoxyspergualin, mizaribine, mycophenolic acid morpholino ester, cyclosporin, FK-506, rapamycin and FTY720.

The present compounds, including salts and hydrates thereof, are useful in the treatment of autoimmune diseases, including the prevention of rejection of bone marrow transplant, foreign organ transplants and/or related afflictions, diseases and illnesses.

The compounds disclosed herein can be administered by any means that effects contact of the active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration, can be oral, topical, including transdermal, ocular, buccal, intranasal, inhalation, intravaginal, rectal, intracisternal and parenteral. The term "parenteral" as used herein refers to modes of administration which include subcutaneous, intravenous, intramuscular, intraarticular injection or infusion, intrasternal and intraperitoneal.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 0.1-2000 milligrams per day. Ordinarily, from 1 to 100 milligrams per day in one or more applications is effective to obtain desired results. These dosages are the effective amounts for the treatment of autoimmune diseases, the prevention of rejection of foreign organ transplants and/or related afflictions, diseases and illnesses.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The active ingredient can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the active ingredient as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene gycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

For administration by inhalation, the compounds disclosed herein may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders

which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of the present invention in suitable propellants, such as fluorocarbons or hydrocarbons.

For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percent solution or suspension of the compounds of the present invention in an appropriate ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

CAPSULES

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

SOFT GELATIN CAPSULES

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

TABLETS

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

INJECTABLE

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

SUSPENSION

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the compounds of this invention are administered stepwise or in conjunction with another therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility of the combined drugs. Thus the term coadministration is understood to include the administration of the two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the two active components.

Methods for preparing the compounds of this invention are illustrated in the following schemes and examples. Alternative routes will be easily discernible to practitioners in the field.

In the tables that follow, any NMR data follows the compounds:

PREPARATION OF N-BENZYL PYRROLIDINE AND N-BENZYL AZETIDINE CARBOXYLATES, PHOSPHINATES AND PHOSPHANATES

Examples I-LVIII have the following structures:

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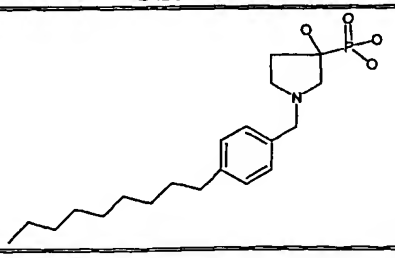
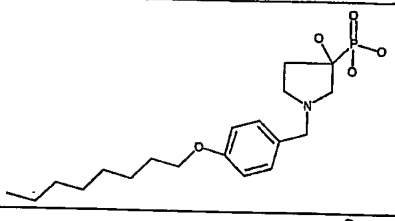
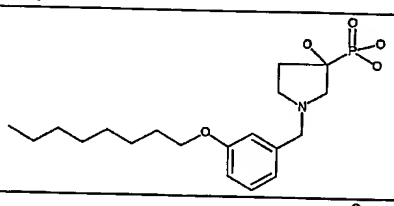
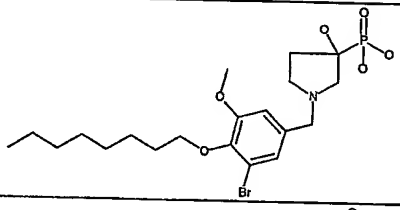
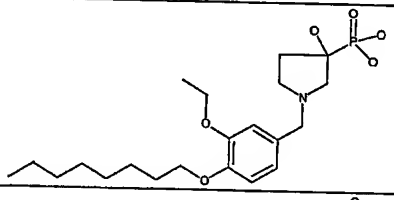
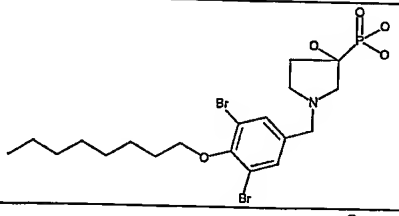
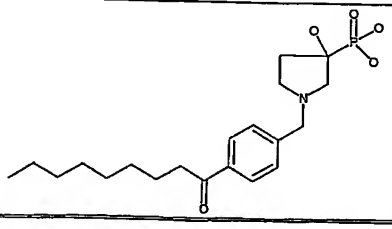
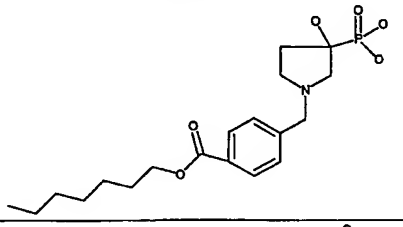
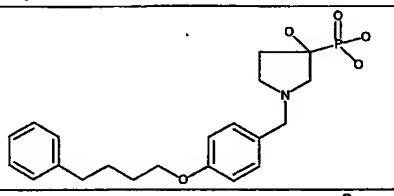
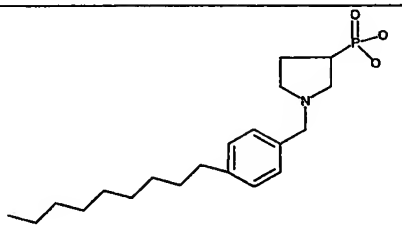
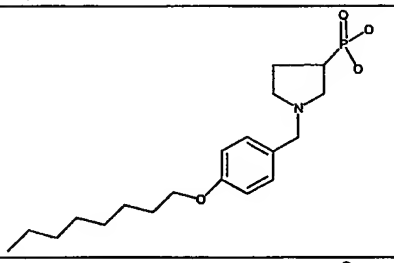
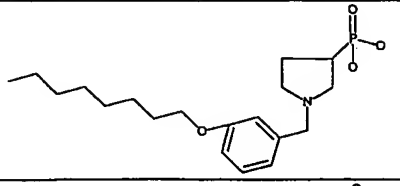
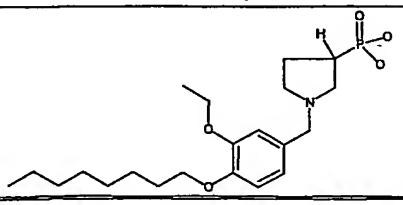
I	

Example No.	Structure
II	
III	
IV	
V + VI	
VII	
VIII	

Example No.	Structure
IX	
X	
XI	
XII	
XIII	
XIV	

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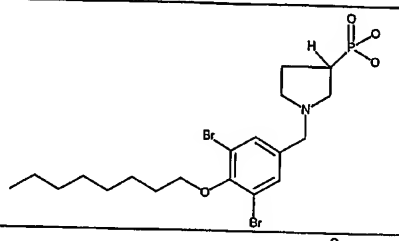
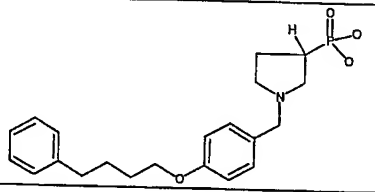
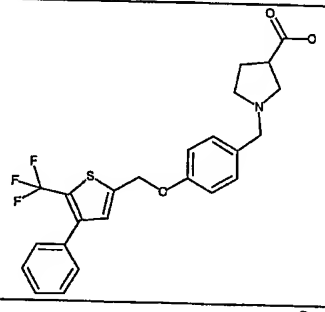
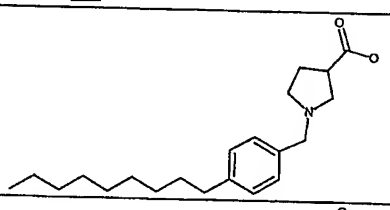
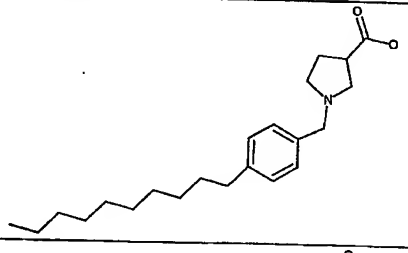
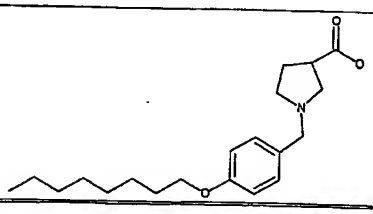
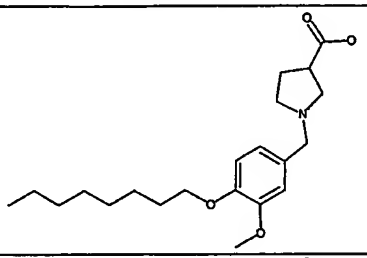
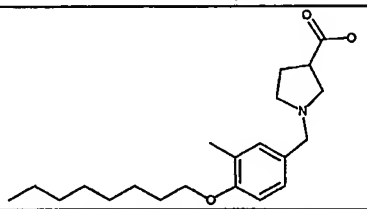
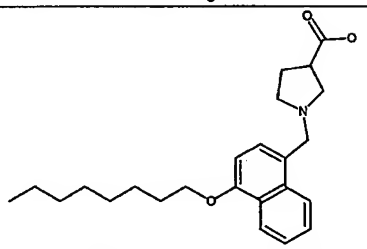
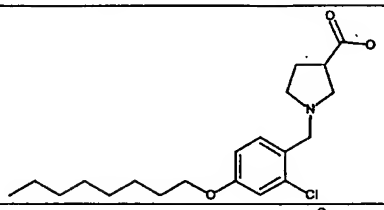
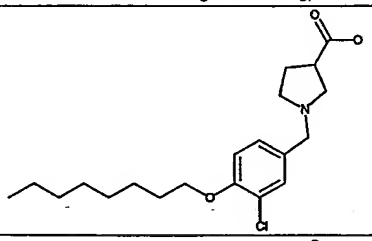
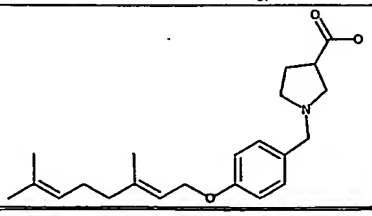
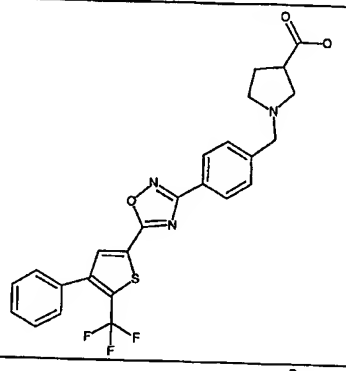
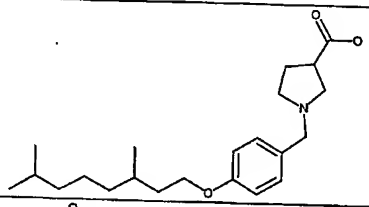
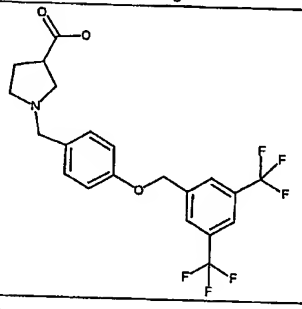
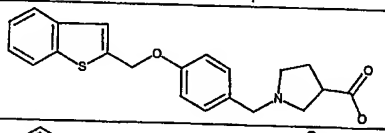
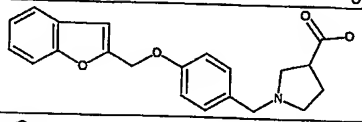
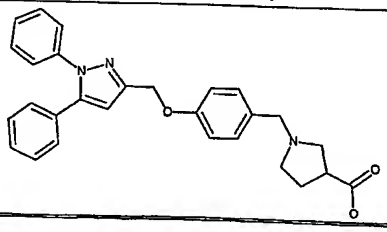
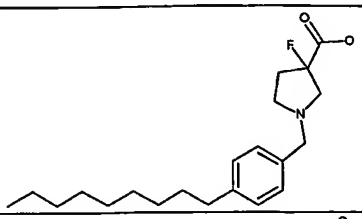
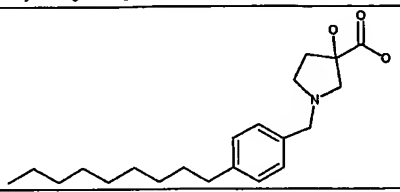
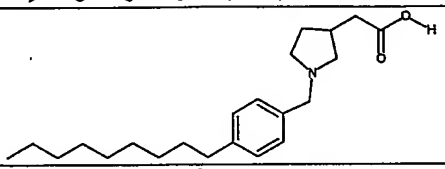
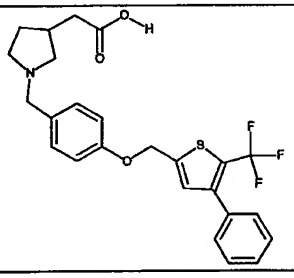
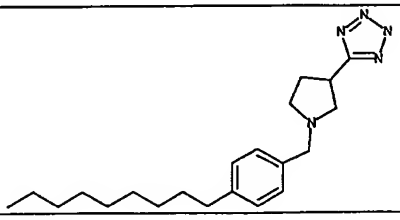
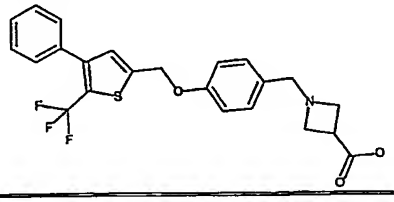
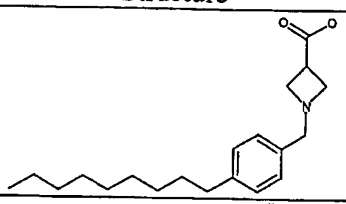
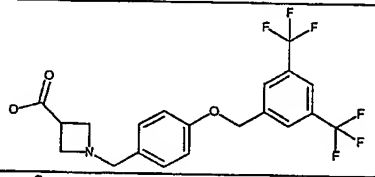
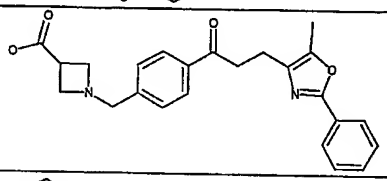
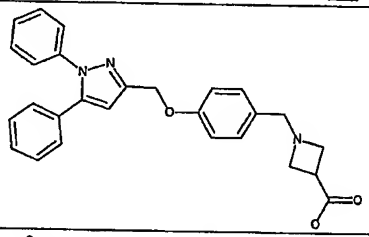
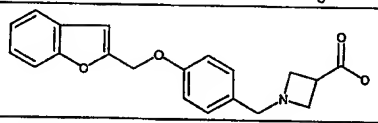
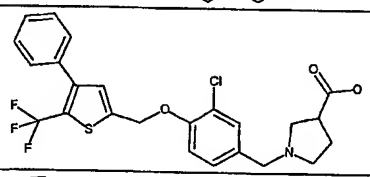
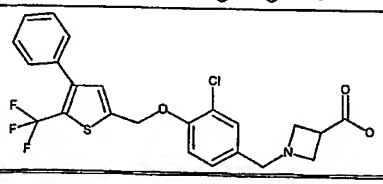
XV + XVI	
XVII	
XVIII	
XIX	
XX	
XXI	

Example No.	Structure
XXII	
XXIII	
XXIV	
XXV	
XXVI	
XXVII	

Example No.	Structure
XXVIII	
XXIX	
XXX	
XXXI	
XXXII	
XXXIII	

Example No.	Structure
XXXV	
XXXVI	
XXXVII	
XXXVIII	
XXXIX	
XL	

Example No.	Structure
XLI	
XLII	
XLIII	
XLIV	
XLV	
XLVI	
XLVII	

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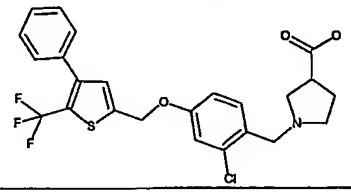
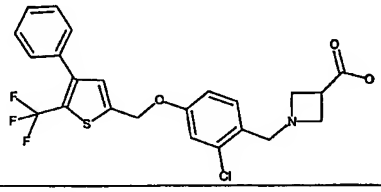
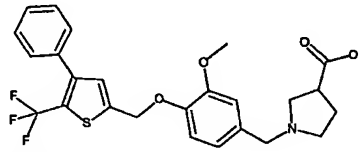
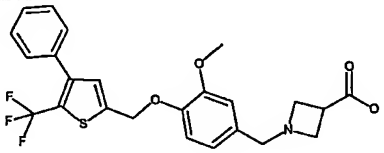
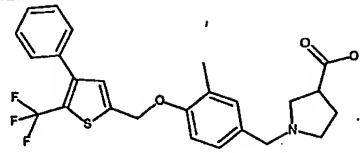
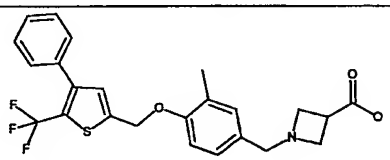
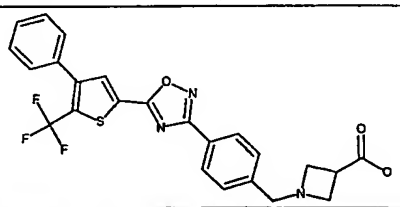
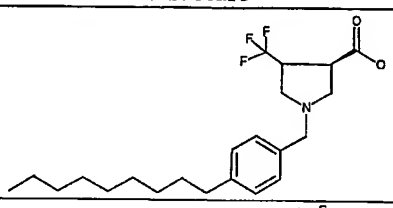
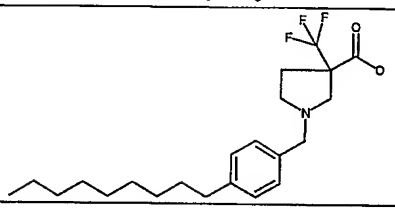
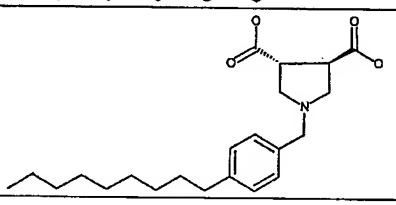
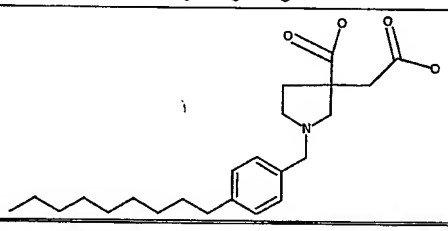
XLVIII	
XLIX	
L	
LI	
LII	
LIII	
LIV	

Example No.	Structure
LV	
LVI	
LVII	
LVIII	

GENERAL

Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Conventional flash chromatography was carried out on silica gel (230-400 mesh). Flash chromatography was also carried out using a Biotage Flash Chromatography apparatus (Dyax Corp.) on silica gel (32-63 mM, 60 Å pore size) in pre-packed cartridges of the size noted. NMR spectra were obtained in $CDCl_3$ solution unless otherwise noted. Coupling constants (J) are in hertz (Hz). Abbreviations: diethyl ether (ether), triethylamine (TEA), N,N-diisopropylethylamine (DIEA) sat'd aqueous (sat'd), rt (rt), hour(s) (h), minute(s) (min).

HPLC CONDITIONS

LC-1: Waters Xterra MS C18, 5 μ, 4.6 x 50 mm column, 10:90 to 95:5 v/v CH_3CN/H_2O + 0.05% TFA over 4.5 min, hold 1 min, PDA detection 200-600 nm, flow rate = 2.5 mL/min.

LC-2: Analytical Sales and Service Armor C8 5 μ 20 x 100 mm column, 10:90 to 90:10 v/v CH_3CN/H_2O + 0.05% TFA over 12 min, hold 4 min, UV detection at either 210 or 254 nM, flow rate = 10 mL/min.

PREPARATION OF ALDEHYDE INTERMEDIATES

Aldehyde I

4-Nonylbenzaldehyde

A solution of 2.0 g (7.5 mmol) of 4-nonylbenzoyl chloride in 75 mL of THF at –78 °C was treated with 7.5 mL (7.5 mmol) of 1M lithium tri-(tert-butoxy) aluminum hydride in THF. After 30 min at –78 °C, the reaction was quenched with 2N HCl and was allowed to warm to rt. The mixture was poured into Et_2O and washed with 2N HCl, sat'd $NaHCO_3$ and sat'd NaCl. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified on a 40M Biotage column using 100:1 v/v hexane/Et_2O as the eluant to afford 708 mg (41%) of the title compound: ^{1}H-NMR (500 MHz) δ 0.87 (t, J = 7.0, 3H), 1.26-1.31 (m, 12H), 1.60-1.66 (m, 2H), 2.68 (t, J = 7.8, 2H), 7.32 (d, J = 8.0, 2H), 7.79 (d, J = 8.0, 2H), 9.97 (s, 1H).

Aldehyde II

4-Decylbenzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde II substituting 4-decylbenzoyl chloride for 4-nonylbenzoyl chloride: ^{1}H-NMR (500 MHz) δ 0.87 (t, J = 6.9, 3H), 1.25-1.31 (m, 14H), 1.60-1.66 (m, 2H), 2.68 (t, J = 7.7, 2H), 7.33 (d, J = 8.0, 2H), 7.79 (d, J = 8.0, 2H), 9.97 (s, 1H).

Aldehyde III

3-(Octyloxy)benzaldehyde

A mixture of 1.00 g (0.82 mmol) of 3-hydroxybenzaldehyde, 1.70 g (12.2 mmol) of potassium carbonate and 2.16 g (9.00 mmol) of 1-iodooctane were warmed in acetonitrile at 80 °C for 16 h. The reaction was cooled, filtered and concentrated. The residue was purified using flash chromatography using 20:1 v/v hexane/ethyl acetate to afford 1.63 g of the title compound as a colorless oil: ^{1}H-NMR (500 MHz) δ 0.89 (t, J = 6.9, 3H), 1.24-1.39 (m, 8H), 1.42-1.50 (m, 2H), 1.80 (m, 2H), 4.01 (t, J = 6.6, 2H), 7.19 (m, 1H), 7.40 (s, 1H), 7.44-7.46 (m, 2H), 9.99 (s, 1H).

Aldehyde IV

4-(Octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ^{1}H NMR (500 MHz) δ 0.91 (t, J = 6.9, 3H), 1.29-1.41 (m, 8H), 1.46-1.52 (m, 2H), 1.71-1.86 (m, 2H), 4.06 (t, J = 6.6, 2H), 7.01 (d, J = 8.7, 2H), 7.85 (d, J = 8.7, 2H), 9.90 (s, 1H).

Aldehyde V

3-Bromo-5-methoxy-4-octyloxybenzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3-bromo-4-hydroxy-5-methoxybenzaldehyde for 3-hydroxybenzaldehyde: ESI-MS: 343 (M+H)

Aldehyde VI

3-Ethoxy-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3-ethoxy-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ^{1}H-NMR (500 MHz) δ 0.88-0.98 (m, 3H), 1.30-1.41 (m, 8H), 1.46-1.51 (m, 5H), 1.85-1.91 (m, 2H), 4.06-4.18 (m, 4H), 6.97 (d, J = 8.0, 1H), 7.39-7.44 (m, 2H), 9.84 (s, 1H); ESI-MS 279.1 (M+H).

Aldehyde VII

3,5-Dibromo-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3,5-dibromo-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde.

Aldehyde VIII

3-Methoxy-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3-methoxy-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ESI-MS 265.2 (M+H)

Aldehyde IX

3-Methyl-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3-methyl-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde.

Aldehyde X

4-(Octyloxy)-1-naphthaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 4-hydroxy-1-naphthaldehyde for 3-hydroxybenzaldehyde.

Aldehyde XI

2-Chloro-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 2-chloro-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ESI-MS 269.0 (M+H)

Aldehyde XII

3-Chloro-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3-chloro-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde.

Aldehyde XIII

4-(*trans*-3,7-Dimethyl-2,6-octadien-1-yloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III using 4-hydroxybenzaldehyde and geranyl bromide: R_F: 0.29 (19:1 v/v hexane/EtOAc); ^{1}H-NMR (500 MHz) δ 1.58-1.83 (m, 9H), 2.00-2.16 (m, 4H), 4.65 (d, J = 6.6, 2H), 5.10 (m, 1H), 5.50 (m, 1H), 7.02 (d, J = 8.7, 2H), 7.85 (d, J = 8.7, 2H), 9.90 (s, 1H).

Aldehyde XIV

4-[Bis(3,5-trifluoromethyl)benzyloxy]benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III using 4-hydroxybenzaldehyde and bis(3,5-trifluoromethyl)benzyl bromide: R_F: 0.28 (9:1 v/v hexane/EtOAc); ^{1}H-NMR (500 MHz) δ 5.28 (s, 2H), 7.14 (d, J = 8.7, 2H), 7.91-7.95 (m, 5H), 9.95 (s, 1H).

Aldehyde XV

3-(4-(Formyl)phenyl)-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

Step A: (E/Z)-2-Phenyl-3-chloro-4,4,4-trifluoro-2-butanal

Phosphorous oxychloride (7.5 mL, 80 mmol) was added to 15 mL of DMF at 0 °C. The resulting mixture was warmed to rt and stirred for 1 h. A solution of 5.0 g (26.6 mmol) of 1,1,1-trifluoromethyl-3-phenyl-2-propanone in 1 mL of DMF was added and the resulting mixture was stirred at 70 °C for 20 h. The reaction mixture was cooled to rt, poured onto 150 g of ice and stirred at ambient temperature for 1 h. The quenched mixture was extracted with 200 mL of ether. The extract was washed with 200 mL of water, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (4L) as the eluant afforded 5.1 g (82%) of the title compound.

Step B: Ethyl (4-phenyl-5-trifluoromethyl)thiophene-2-carboxylate

Ethyl mercaptoacetate (2.75 mL, 25.0 mmol) was added to a suspension of 600 mg (25 mmol) of NaH in 45 mL of THF maintaining the internal temperature at 25 °C. A solution of 5.10 g (21.7 mmol) of (E/Z)-2-phenyl-3-chloro-4,4,4-trifluoro-2-butanal (from Step A) was added and the resulting mixture was stirred at rt for 20 h. The reaction was quenched with 50 mL of sat'd NH_4Cl and the resulting mixture was partitioned between 250 mL of ether and 100 mL of water. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (1L), then 4:1 v/v hexanes/CH_2Cl_2 (1L) as the eluant afforded 5.10 g (78%) of the title compound: ^1H NMR (400 Mhz) δ 1.40 (t, J= 7.2, 3H), 4.39 (q, J= 7.2, 2H), 7.42 (app s, 5H), 7.74 (q, J=1.6, 1H).

Step C: (4-Phenyl-5-trifluoromethyl)thiophene-2-carboxylic acid

A solution of 5.10 g (17.0 mmol) of ethyl 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylate (from Step B) in 20 mL of EtOH was treated with 10 mL of 5.0 N NaOH and stirred at rt for 30 min. The EtOH was removed in vacuo. The residual aqueous mixture was acidified to pH 2 with 1 N HCl, then extracted with 300 mL of 1:1 v/v EtOAc/ether. The extract was separated, dried and concentrated. Recrystallization from 200 mL of 20:1 v/v hexanes/ether afforded 4.30 g (93%) of the title compound: ^1H NMR (500 Mhz) δ 7.43 (app s, 5H), 7.84 (app s, 1H); ^{13}C NMR ($CDCl_3$, 125 Mhz) δ 121.7 (q, J= 269), 128.5, 128.6, 128.8, 132.5 (q, J= 36), 133.3, 133.8, 137.5, 144.8, 167.0.

Step D: 3-[4-(Carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 408 mg (1.5 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid and 1 mL of oxalyl chloride in 5 mL of CH_2Cl_2 was treated with 5 drops of DMF. The resulting mixture was stirred at rt for 1 h, then concentrated. The crude acid chloride and 291 mg (1.5 mmol) of 4-(carbomethoxy)benzamidoxime were dissolved in 7 mL of 6:1 v/v xylenes/pyridine. The resulting solution was heated at 140 °C for 1 h, then cooled. The mixture was partitioned between 50 mL of 1:1 EtOAc/ether and 50 mL of 1 N HCl. The organic layer was separated, washed with 3 x 50 mL of 1 N HCl, 50 mL of sat'd $NaHCO_3$, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes

(1L), then 20:1 v/v hexanes/EtOAc (1L) as the eluant afforded 423 mg (65%) of the title compound: ^{1}H NMR (500 Mhz) δ 3.97 (s, 3H), 7.48 (app s, 5H), 7.92 (s, 1H), 8.18 (app d, J= 8.5, 2H), 8.23 (app d, J= 8.5, 2H).

Step E: 3-[4-(Hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 390 mg (0.91 mmol) of 3-[4-(carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step D) in 10 mL of CH_2Cl_2 at –78 °C was treated with 2.7 mL of 1.0 M DIBALH solution in CH_2Cl_2. The resulting solution was stirred cold for 1 h, then quenched with 5 mL of sat'd Rochelle salt solution. The mixture was partitioned between 100 mL CH_2Cl_2 and 50 mL of 1 N NaOH. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 S cartridge using 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 325 mg (89%) of the title compound: ^{1}H NMR (500 Mhz) δ 1.80 (app s, 1H), 4.80 (d, J= 4.0, 2H), 7.46-7.48 (5H), 7.52 (d, J= 8.0, 2H), 7.91 (q, J= 1.5, 1H), 8.14 (d, J= 8.0, 2H).

Step F: 3-[4-(Formyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A mixture of 310 mg (0.77 mmol) of 3-[4-(hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step E), 527 mg (1.5 mmol) of 4-methylmorpholine N-oxide and 500 mg of 4 A molecular sieves in 15 mL of CH_3CN was treated with 12 mg (0.034 mmol) of tetrapropylammonium perruthnate and the resulting mixture was stirred ar rt for 2 h. The solids were filtered and the filtrated was concentrated. Chromatography on a Biotage 40 S cartridge using 9:1 v/v hexanes/EtOAc (1L) as the eluant afforded 205 mg (66%) of the title compound: ^{1}H NMR (500 Mhz) δ 7.48 (app s, 5H), 7.93 (app s, 1H), 8.03 (d, J= 8.5, 2H), 8.33 (d, J= 8.5, 2H), 10.1 (s, 1H).

Aldehyde XVI

4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzaldehyde

Step A: 2-Hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene

A solution of 2.10 g (7.7 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid (from Aldehyde XV, Step C) in 20 mL of THF was treated with 5.0 mL of 2.0 M borane dimethylsulfide complex in THF. The resulting solution was heated at reflux for 3 h, cooled to rt, quenched with 10 mL of MeOH and concentrated. Chromatography on a Biotage 40M cartridge using 9:1 v/v hexanes/EtOAc as the eluant afforded 1.95 g (98%) of the title compound: ^{1}H NMR (500 Mhz) δ 2.05 (app s, 1H), 4.87 (s, 2H), 6.99 (s, 1H), 7.41 (app s, 5H).

Step B: 4-((4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

A solution of 1.95 g (7.5 mmol) of 2-hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene (from Step A), 925 mg (7.6 mmol) of 4-hydroxybenzaldehyde and 3.0 g (11.4 mmol) of triphenylphosphene in 40 mL of THF at 0 °C was treated with 2.0 g (11.4 mmol) of diethylazodicarboxylate. The resulting mixture was warmed to rt, stirred for 2 h, then concentrated. Chromatography on a Biotage 75S cartridge using 9:1 v/v heptane/EtOAc as the eluant afforded 2.5 g of impure title compound. Chromatography on a Biotage 40M cartridge using 19:1 v/v hexanes/EtOAc (1L), then 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 1.65 g (60%) of the title compound: ^{1}H NMR (500 Mhz) δ 5.32 (s, 2H), 7.10 (d, J= 8.5, 2H), 7.12 (s, 1H), 7.41-7.43 (5H), 7.85-7.90 (2H), 9.92 (s, 1H).

Aldehydes 17-21 were prepared using procedures analogous to those described in Aldehyde 16 substituting the appropriately substituted benzaldehyde for 4-(hydroxy)benzaldehyde in Step B:

Aldehyde XVII

3-((4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde XVIII

2-Chloro-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde XIX

3-Chloro-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde XX

3-Methyl-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde XXI

3-Methoxy-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde XXII

4-(4-Phenylbutoxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde IV substituting 4-(iodobutyl)benzene for 1-iodooctane: ESI-MS 255.2 (M+H)

Aldehyde XXIII

4-(Non-1-oyl)benzaldehyde

Step A: 4-(1-Hydroxynon-1-yl)benzaldehyde

Terephthaldicarboxaldehyde (2.00 g, 14.91 mmol) was dissolved in tetrahydrofuran (25 ml) and cooled to 0°C. Octylmagnesium chloride (7.5 ml, 2.0M in THF, 15 mmol) was added dropwise. After 15 minutes, the reaction was quenched with 2N aqueous hydrochloric acid (50 ml) and diluted with ethyl acetate (50 ml). The organic layer was separated, washed with sat'd NaCl (50 ml), dried over magnesium sulfate and concentrated . Silica gel chromatography eluting with 91:9 v/v hexane/EtOAc gave 0.19 g (0.77 mmol, 5.1%) of the title compound: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.87 (d, J = 8.0, 2H), 7.52 (d, J = 8.3, 2H), 4.75-4.80 (m, 1H), 1.68-1.82 (m, 2H), 1.22-1.45 (m, 12H), 0.91 (t, J = 7.0, 3H).

Step B: 4-(Non-1-oyl)benzaldehyde

Dess-Martin periodinane (0.268 g, 0.632 mmol) was added to a solution of 4-(1-hydroxynon-1-yl)benzaldehyde (0.125 g, 0.505 mmol) from Step A in CH_2Cl_2 (3.0 ml). After 1 h, the reaction was filtered and concentrated. Silica gel chromatography eluting with 19:1 v/v hexane/EtOAc gave 0.107 g (0.446 mmol, 88%) of the title compound: ^{1}H NMR (500 MHz) δ 10.1 (s, 1H), 8.10 (d, J = 8.2,

2H), 7.97 (d, J = 8.2, 2H), 3.00 (t, J = 7.3, 2H), 1.70-1.8 (m, 2H), 1.22-1.42 (m, 10H), 0.88 (t, J = 7.0, 3H).

Aldehyde XXIV

Heptyl 4-(formyl)benzoate

The title compound was prepared through a condensation between 1-heptanol and 4-formylbenzoic acid. ^{1}H NMR (500 MHz , $CDCl_3$): δ 10.10 (s, 1H), 8.20 (d, J = 8.2, 2H), 7.95 (d, J = 8.2, 2H), 4.35 (t, J = 6.8, 2H), 1.75-1.85 (m, 2H), 1.40-1.50 (m, 2H), 1.25-1.40 (m, 6H), 0.89 (t, J = 7.0, 3H).

Aldehydes XXV and XXVI were prepared using procedures analogous to those described in Aldehyde 16 substituting the appropriately substituted alcohol for 2-hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene in Step B:

Aldehyde XXV

4-[(Benzothien-2-yl)methoxy]benzaldehyde

^{1}H NMR (500 MHz) δ 5.34 (s, 2H), 7.04 (d, J = 8.7, 2H), 7.18 (s, 1H), 7.25-7.30 (m, 4H), 7.76 (d, J = 8.7, 2H), 9.82 (s, 1H).

Aldehyde XXVI

4-[(2,3-Diphenyl-2H-pyrazol-5-yl)methoxy]benzaldehyde

^{1}H NMR (500 MHz) δ 5.21 (s, 2H), 6.55 (s, 1H), 7.10 (d, J = 8.7, 2H), 7.14-7.17 (m, 5H), 7.21-7.30 (m, 5H), 7.79 (d, J = 8.7, 2H), 9.82 (s, 1H).

PREPARATION OF EXAMPLES

EXAMPLE I

(R/S)-1-(4-(Nonyl)phenyl)methyl-3-hydroxy-pyrrolidin-3-yl)phosphonic acid

Step A: (R/S)-1-tert-Butoxycarbonyl-3-hydroxypyrrolidine

A solution of 2.5 g (28.7 mmol) of (R/S)-3-hydroxypyrrolidine in 10 mL of CH_2Cl_2 at 0 °C was treated with 6.89 g (31.6 mmol) of di-tert-butyl-dicarbonate in 2 mL CH_2Cl_2 and 0.35 g (2.8 mmol) of 4-(N,N-dimethylamino) pyridine. After stirring for 10 min, the reaction was warmed to rt and stirred overnight. The reaction was diluted with 100 mL of CH_2Cl_2 and washed with 100 mL of 1N HCl and 100 mL of 1N $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a 40M Biotage column using 7:3 v/v hexane/acetone as the eluant to afford 5.3 g (99%) of the title compound: R_F: 0.26 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.45 (s, 9H), 1.88-2.00 (m, 2H), 2.52 (br s, 1H), 3.29-3.50 (m, 4H), 4.42 (m, 1H).

Step B: 1-tert-Butoxycarbonyl-3-oxo-pyrrolidine

A solution of 2.3 mL (26 mmol) of oxalyl chloride in 80 mL of CH_2Cl_2 at -78 °C was treated with 3.8 mL (53 mmol) of DMSO in 5 mL of CH_2Cl_2. The resulting mixture was stirred cold for 5 min. A solution of 2.0 g (10.7 mmol) of (R/S)-1-tert-butoxycarbonyl-3-hydroxypyrrolidine (from Step A) in 10 mL of CH_2Cl_2 was added. The resulting mixture was stirred for 30 min, treated with 18.7 mL (107 mmol) of DIEA and warmed to 0 °C. After stirring for 45 min, the reaction was quenched with H_2O and poured into 100 mL of 1N HCl. After separating the layers, the organic layer was washed with 100 mL sat'd NaCl, dried over Na_2SO_4 and concentrated. The residue was purified on a 40M Biotage column using 4:1 v/v hexane/acetone as the eluant to afford 1.9 g (96%) of the title compound: R_F: 0.49 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.48 (s, 9H), 2.58 (t, J = 7.9, 2H), 3.71-3.78 (m, 4H).

Step C: (R/S)-1-tert-Butoxycarbonyl-3-hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester

A mixture of 1.9 g (10.3 mmol) of 1-tert-butoxycarbonyl-3-oxopyrrolidine (from Step B), 1.3 mL (10.3 mmol) of diethyl phosphite and 1.4 mL (10.3 mmol) of TEA was stirred at 100 °C for 1.5 h. Volatiles were removed under reduced pressure. The residue was purified on a 40M Biotage column using 13:7 v/v hexane/acetone as the eluant to afford 1.78 g (53%) of the title compound as a yellow

oil: R_F: 0.16 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.33 (t, J = 7.0, 6H), 1.45 (s, 9H), 2.08 (m, 1H), 2.18 (m, 1H), 3.47-3.64 (m, 4H), 4.13-4.22 (m, 4H).

Step D: (R/S)-3-Hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester

A solution of 1.78 g (5.5 mmol) of (R/S)-1-tert-butoxycarbonyl-3-hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester (from Step C) in 2N HCl in EtOH was stirred at rt for 5.5 h. The reaction was concentrated from CH_2Cl_2 several times. The crude product was partitioned between aqueous NH_4OH and $CHCl_3$/isopropanol (3:1 v/v). After separating phases, the aqueous layer was extracted with 3X $CHCl_3$/isopropanol (3:1 v/v). The combined organics were dried over Na_2SO_4 and concentrated. The residue was purified on a 40S Biotage column using 90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford the title compound as a light brown oil: ^{1}H-NMR (500 MHz) δ 1.35 (t, J = 7.0, 6H), 1.92 (m, 1H), 2.20 (m, 1H), 2.78-2.99 (m, 3H), 3.06 (dd, J = 12.7, 3.7, 1H), 3.13 (dd, J = 12.7, 6.2, 1H), 3.20 (m, 1H), 4.16-4.23 (m, 4H).

Step E: (R/S)-1-(4-(Nonylphenyl)methyl-3-hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester

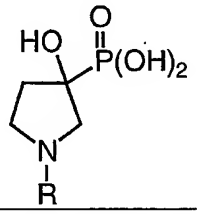
A solution of 60 mg (0.23 mmol) of (R/S)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester (from Step D) and 54 mg (0.23 mmol) of Aldehyde I in 1.5 mL of CH_2Cl_2 was treated with 73 mg (0.34 mmol) of sodium triacetoxyborohydride. After 3 h at rt, the reaction was diluted with 25 mL of CH_2Cl_2 and washed with 25 mL of 1N $NaHCO_3$. After separating phases, the aqueous layer was extracted with 25 mL of CH_2Cl_2. The combined organic layers were washed with 50 mL of sat'd NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography using 3:1 v/v hexane/acetone as the eluant to afford 33 mg (32%) of the title compound: R_F: 0.31 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.89 (t, J = 7.0, 3H), 1.27-1.36 (m, 18H), 1.57-1.63 (m, 2H), 1.97 (m, 1H), 2.41-2.54 (m, 2H), 2.59 (t, J = 7.7, 2H), 2.85-2.92 (m, 2H), 3.01 (m, 1H), 3.67 (ABq, J = 13.1, 2H), 4.16-4.23 (m, 4H), 7.12 (d, J = 7.8, 2H), 7.24 (d, J = 7.8, 2H).

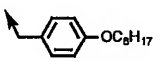
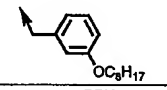
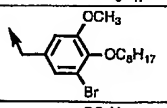
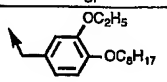
Step F: (R/S)-1-(4-Nonylbenzyl)-3-hydroxypyrrolidin-3-ylphosphonic acid

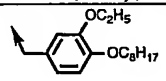
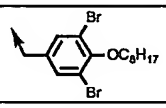
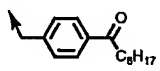
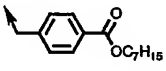
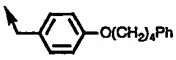
A solution of 33 mg (0.075 mmol) of (R/S)-1-(4-nonylbenzyl)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester (from Step E) in 1 mL of chloroform was treated with 0.053 mL (0.37 mmol) of iodotrimethylsilane. The reaction was allowed to stir at rt for 1h. The reaction was quenched with MeOH and concentrated several times from MeOH. The residue was purified using LC-2 to afford 4.6 mg (16%) of the title compound: ESI-MS 385 (M+H); LC-1: 3.01 min.

EXAMPLES II-X

EXAMPLES II-X were prepared using procedures analogous to those described in EXAMPLE I substituting the appropriate Aldehyde in Step E. TMS-Br was substituted in Step F with substrates containing TMS-I sensitive functionality (See EXAMPLE 11, Step D). In EXAMPLES V and VI enantiomers were resolved after Step E by preparative chiral HPLC (Chiralpak AD 2 x 25 cm HPLC column, 9:1 v/v hexane/EtOH, flow rate = 9.0 mL/min, λ = 210 nM).



EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
II		LC-1	2.7	386
III		LC-1	2.7	386
IV		LC-1	3.0	496
V Enantiomer 1		LC-1	2.8	430

^{1}H-NMR (500 MHz, CD_3OD) δ 0.92 (t, J = 7.0, 3H), 1.20-1.54 (m, 9H), 1.79-1.84 (m, 2H), 2.23 (m, 1H), 2.35 (m, 1H), 2.43 (m, 1H), 2.68 (m, 1H), 3.41-3.50 (m, 2H), 3.58 (m, 1H), 3.68 (m, 1H), 3.75-3.79 (m, 2H), 4.04 (t, J = 6.4, 2H), 4.11-4.15 (m, 2H), 4.38 (ABq, J = 12.9, 2H), 7.02-7.09 (m, 2H), 7.17 (s, 1H)				
VI Enantiomer 2		LC-1	2.8	430
VII		LC-1	3.1	544
^{1}H-NMR (500 MHz, CD_3OD) δ 0.93 (t, J = 6.8, 3H), 1.20-1.46 (m, 9H), 1.55-1.61 (m, 2H), 1.86-1.92 (m, 2H), 2.23-2.35 (m, 2H), 2.72 (m, 1H), 3.47-3.79 (br m, 3H), 4.06 (t, J = 6.4, 2H), 4.44-4.50 (m, 2H), 7.86 (s, 2H)				
VIII		LC-1	2.6	398
IX		LC-1	2.5	400
X		LC-1	2.4	406

EXAMPLE XI

(R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl phosphonic acid

Step A: (R/S)-1-Benzyl-pyrrolidin-3-yl phosphonic acid, diethyl ester

A solution of 6.0 g (36.6 mmol) of diethyl vinylphosphonate and 11 mL (44 mmol) of N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine in 150 mL of CH_2Cl_2 at 0 °C was stirred for 30 min. The reaction mixture was washed with 150 mL of 1N $NaHCO_3$ and 150 mL of sat'd NaCl. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a 40L Biotage column using 3:2 and 1:1 v/v hexane/acetone as the gradient to afford 9.44 g (87%) of the title

compound as a pale yellow oil: R_F: 0.24 (3:2 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.32 (t, J = 7.0, 6H), 2.04-2.12 (m, 2H), 2.39-2.58 (m, 3H), 2.83 (m, 1H), 2.97 (m, 1H), 3.64 (s, 2H), 4.06-4.16 (m, 4H), 7.24-7.34 (m, 5H); ESI-MS 298 (M+H); LC-1: 1.2 min.

Step B: (R/S)-Pyrrolidin-3-ylphosphonic acid, diethyl ester

A mixture of 3 g (10 mmol) of (R/S)-1-benzyl-pyrrolidin-3-ylphosphonic acid, diethyl ester (from Step A), 9.5 g (150 mmol) of ammonium formate and 1.0 g of 10% palladium on charcoal in 60 mL of MeOH was warmed to 40 °C for 1.5 h. The reaction was cooled, filtered through a pad of celite and concentrated. The mixture was partitioned between 75 mL of 1N NaOH and 100 mL of CH_2Cl_2. After separating layers, the aqueous phase was extracted with 3X100 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified on a 40M Biotage column using 90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford the title compound as a pale yellow oil: R_F: 0.13 (95:5:0.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz) δ 1.22 (t, J = 7.1, 6H), 1.81 (m, 1H), 1.95 (m, 1H), 2.25 (m, 1H), 2.73 (m, 1H), 2.89-2.99 (m, 3H), 4.06-4.16 (m, 4H).

Step C: (R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-ylphosphonic acid, diethyl ester

A solution of 41 mg (0.19 mmol) of (R/S)-pyrrolidin-3-yl phosphonic acid, diethyl ester (from Step B) and 43 mg (0.18 mmol) of Aldehyde I in 1 mL of CH_2Cl_2 was treated with 57 mg (0.27 mmol) of sodium triacetoxyborohydride. After stirring at rt overnight, the reaction was diluted with 25 mL of CH_2Cl_2 and washed with 25 mL of 1N $NaHCO_3$. After separating phases, the aqueous layer was extracted with 25 mL of CH_2Cl_2. The combined organic layers were washed with 50 mL of sat'd NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography using 49:1 v/v CH_2Cl_2/MeOH as the eluant to afford 67 mg (99%) of the title compound: R_F: 0.39 (19:1 v/v CH_2Cl_2/MeOH); ^{1}H-NMR (500 MHz) δ 0.90 (t, J = 7.0, 3H), 1.20-1.35 (m, 17H), 1.59-1.65 (m, 2H), 2.04-2.13 (m, 3H), 2.41-

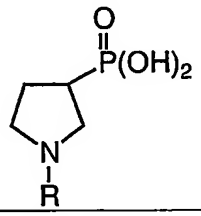
2.62 (m, 5H), 2.85 (m, 1H), 2.99 (m, 1H), 3.62 (s, 2H), 4.08-4.17 (m, 4H), 7.14 (d, J = 8.0, 2H), 7.24 (d, J = 8.0, 2H).

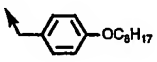
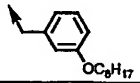
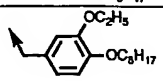
Step D: (R/S)-1-(4-Nonylbenzyl)-pyrrolidin-3-ylphosphonic acid

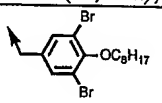
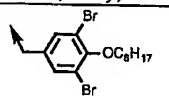
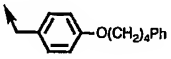
A solution of 67 mg (0.16 mmol) of (R/S)-1-(4-nonylbenzyl)-pyrrolidin-3-ylphosphonic acid, diethyl ester (from Step C) in 1 mL of acetonitrile was treated with 0.094 mL (0.71 mmol) of bromotrimethylsilane. The reaction was allowed to stir at 80 °C for 1h. The reaction was quenched with MeOH and concentrated several times from MeOH. The residue was purified by LC-2 to afford 27 mg (46%) of the title compound: ESI-MS 368 (M+H); LC-1: 3.1 min.

EXAMPLES XII-XVII

EXAMPLES XII-XVII were prepared using procedures analogous to those described in EXAMPLE XI substituting the appropriate Aldehyde in Step C. In EXAMPLES XV and XVI enantiomers were were resolved after Step E by preparative chiral HPLC (Chiralcel OD 2 x 25 cm HPLC column, 19:1 v/v hexane/iPrOH, flow rate = 9.0 mL/min, λ = 210 nM).



EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
XII		LC-1	2.8	370
XIII		LC-1	2.7	370
XIV		--	--	--

^{1}H-NMR (500 MHz, CD_3OD) δ 0.92 (t, J = 7.0, 3H), 1.34-1.54 (m, 10H), 1.79-1.84 (m, 2H), 2.18 (m ,1H), 2.32-2.45 (m, 2H), 2.69 (m, 1H), 2.88 (m, 1H), 3.22-3.37 (m, 2H), 3.47-3.62 (m, 2H), 3.73 (m, 1H), 4.04 (t, J = 6.4, 2H), 4.13 (q, J = 7.0, 2H), 4.32-4.37 (m, 2H), 7.02-7.08 (m, 2H), 7.16 (s, 1H)				
XV Enantiomer 1		LC-1	3.2	528
^{1}H-NMR (500 MHz, CD_3OD) δ 0.93 (t, J = 6.9, 3H), 1.34-1.46 (m, 8H), 1.55-1.61 (m, 2H), 1.86-1.95 (m, 2H), 2.25-2.47 (m, 2H), 2.72 (m, 1H), 3.28 (m, 1H), 3.63-3.79 (m, 3H), 4.06 (t, J = 6.4, 2H), 4.44 (s, 2H), 7.87 (s, 2H)				
XVI Enantiomer 2		LC-1	3.1	528
XVII		LC-1	2.4	390

EXAMPLE XVIII

(R/S)-1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-pyrrolidin-3-yl carboxylic acid

Step A: (R/S)-1-Benzyl-pyrrolidin-3-yl carboxylic acid, benzyl ester

A solution of 10.0 g (61.6 mmol) of benzyl acrylate and 19 mL (74.2 mmol) of N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine in 75 mL of CH_2Cl_2 at 0 °C was treated with 0.5 mL (6.5 mmol) of TFA while maintaining the internal temperature at less than 3 °C. The reaction was warmed to rt and stirred for 2.5 h. The reaction mixture was washed with 250 mL of 1N $NaHCO_3$ and 250 mL of sat'd NaCl. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a 40L Biotage column using 19:1 v/v hexane/acetone as the eluant to

afford 18 g (99%) of the title compound as a light yellow oil: R_F: 0.28 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.15-2.20 (m, 2H), 2.60 (m, 1H), 2.73-2.77 (m, 2H), 3.02 (m, 1H), 3.13 (m, 1H), 3.66-3.73 (m, 2H), 5.17 (s, 2H), 7.28-7.42 (m, 5H).

Step B: (R/S)-1-Benzyloxycarbonyl-pyrrolidin-3-yl carboxylic acid, benzyl ester

A solution of 18 g (61 mmol) of (R/S)-1-benzyl-pyrrolidin-3-yl carboxylic acid, benzyl ester (from Step A) in 100 mL of CH_2Cl_2 at 0 °C was treated with 21.3 mL (231 mmol) of benzyl chloroformate while maintaining the internal temperature at less than 6 °C. The reaction was allowed to warm to rt overnight. After 24 hours at rt, an additional 10 mL (10.8 mmol) of benzyl chloroformate was added. After 24 hours of stirring at rt, the reaction was concentrated. The residue was purified on a 40L Biotage column using 19:1 v/v hexane/acetone as the eluant to afford 8.42 g (39%) of the title compound as a colorless oil: R_F: 0.14 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.19-2.22 (m, 2H), 3.15 (m,1H), 3.45-3.75 (m, 4H), 5.13-5.20 (m, 4H), 7.33-7.41 (m, 10H).

Step C: (R/S)-Pyrrolidin-3-yl carboxylic acid

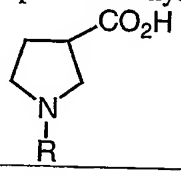
A mixture of 8.4 g (24.7 mmol) of (R/S)-1-benzyloxycarbonyl-pyrrolidin-3-yl carboxylic acid, benzyl ester (from Step B) and 2.86 g of 10% palladium on charcoal in 80 mL of MeOH was hydrogenated at atmospheric pressure using a balloon of hydrogen for 6.5 h. The reaction was filtered through a pad of Celite and concentrated to afford 2.72 g (95%) of the title compound as a white solid: ^{1}H-NMR (500 MHz, CD_3OD) δ 2.17-2.26 (m, 2H), 3.03 (m, 1H), 3.24-3.38 (m, 3H), 3.51 (m, 1H).

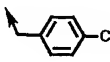
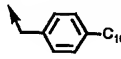
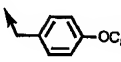
Step D: (R/S)-1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-pyrrolidin-3-yl carboxylic acid

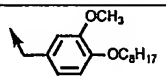
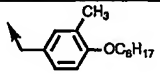
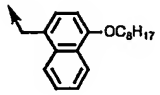
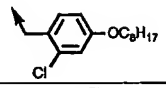
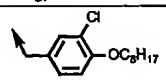
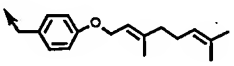
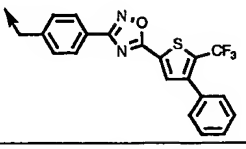
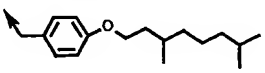
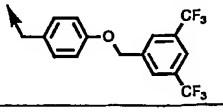
A mixture of 17.5 mg (0.15 mmol) of (R/S)-pyrrolidin-3-yl carboxylic acid (from Step C), 78 mg (0.21 mmol) of Aldehyde XVI and 9 mg (0.14 mmol) of sodium cyanoborohydride in 2 mL of MeOH was stirred at rt overnight. The reaction was concentrated and purified by flash chromatography using 19:1 v/v CH_2Cl_2/MeOH, then 85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford 42 mg (63%) of the title compound as a white foam: R_F: 0.29 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 2.23-2.35 (m, 2H), 3.09 (m, 1H), 3.26-3.41 (m, 3H), 3.53 (m, 1H), 4.30 (ABq, J = 13.0, 2H), 5.38 (s, 2H), 7.13 (d, J = 8.5, 2H), 7.22 (s, 1H), 7.39-7.45 (m, 5H), 7.48 (d, J = 8.5, 2H); ESI-MS 462 (M+H); LC-1: 2.7 min.

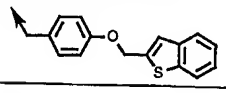
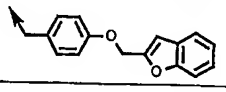
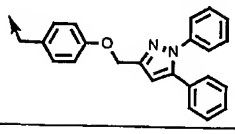
EXAMPLES XIX-XXXIII

EXAMPLES 19-33 were prepared using procedures analogous to those described in EXAMPLE 18 substituting the appropriate Aldehyde in Step D.



EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
XIX		LC-1	2.8	332
^{1}H-NMR (500 MHz) δ 0.91 (t, J = 6.9, 3H), 1.30-1.34 (m, 12H), 1.60-1.63 (m, 2H), 2.33-2.41 (m, 2H), 2.60-2.63 (m, 2H), 3.09-3.29 (m, 4H), 3.73 (m, 1H), 4.20 (ABq, J = 12.5, 2H), 7.21 (d, J = 7.7, 2H), 7.44 (d, J = 7.7, 2H)				
XX		LC-1	3.0	346
XXI		LC-1	3.0	334
^{1}H-NMR (500 MHz, CD_3OD) δ 0.91 (t, J = 7.0, 3H), 1.31-1.50 (m, 10H), 1.75-1.80 (m, 2H), 2.22-2.33 (m, 2H), 3.08 (m, 1H), 3.25-3.40 (m, 3H), 3.52 (m, 1H), 3.99 (t, J = 6.4, 2H), 4.28 (ABq, J = 13.0, 2H), 6.97 (d, J = 8.6, 2H), 7.41 (d, J = 8.6, 2H)				

XXII		LC-1	2.9	364
^{1}H-NMR (500 MHz, CD_3OD) δ 0.91 (t, J = 6.9, 3H), 1.31-1.51 (m, 10H), 1.76-1.82 (m, 2H), 2.24-2.37 (m, 2H), 3.17 (m, 1H), 3.29-3.43 (m, 3H), 3.56 (m, 1H), 3.87 (s, 3H), 4.01 (t, J = 6.5, 2H), 4.29 (ABq, J = 12.8, 2H), 6.98 (d, J = 8.2, 1H), 7.03 (dd, J = 8.2, 1.7, 1H), 7.12 (d, J = 1.7, 1H)				
XXIII		LC-1	3.3	348
XXIV		LC-1	3.5	384
XXV		LC-1	3.2	368
XXVI		LC-1	3.2	368
XXVII		LC-1	2.9	358
XXVIII		LC-1	3.2	500
^{1}H-NMR (500 MHz, CD_3OD) δ 2.26-2.37 (m, 2H), 3.13 (m, 1H), 3.25-3.43 (m, 3H), 3.52 (m, 1H), 4.37 (ABq, J = 12.9, 2H), 7.49-7.50 (m, 5H), 7.69 (d, J = 8.1, 2H), 8.00 (s, 1H), 8.16 (d, J = 8.1, 2H)				
XXIX		LC-1	3.0	362
EXAMPLE XXIX was prepared by catalytic hydrogenation of EXAMPLE 27 using a procedure analogous to that described in EXAMPLE 18, Step C.				
XXX		LC-1	2.9	448

^{1}H-NMR (500 MHz, CD_3OD) δ 2.23-2.34 (m, 2H), 3.09 (m, 1H), 3.25-3.40 (m, 3H), 3.53 (m, 1H), 4.30 (ABq, J = 13.0, 2H), 5.31 (s, 2H), 7.14 (d, J = 8.6, 2H), 7.48 (d, J = 8.6, 2H), 7.94 (s, 1H), 8.07 (s, 2H)				
XXXI		--	--	368
XXXII		--	--	352
XXXIII		--	--	454

EXAMPLE XXXV

(R/S)-1-(4-Nonylphenyl)methyl-3-fluoro-pyrrolidin-3-yl carboxylic acid

Step A: (R/S)-1-Benzyl-pyrrolidin-3-yl carboxylic acid, methyl ester

The title compound was prepared using a procedure analogous to that described in EXAMPLE XVIII, Step A substituting methyl acrylate for benzyl acrylate: R_F: 0.29 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.10-2.14 (m, 2H), 2.55 (m, 1H), 2.66 (m, 1H), 2.75 (m, 1H), 2.94 (m, 1H), 3.06 (m, 1H), 3.65 (s, 2H), 3.69 (s, 3H), 7.25-7.35 (m, 5H).

Step B: (R/S)-Pyrrolidin-3-yl carboxylic acid, methyl ester hydrochloride salt

A solution of 0.52 g (2.3 mmol) of (R/S)-1-benzyl-pyrrolidin-3-yl carboxylic acid, methyl ester (from Step A) in 5 mL of 1,2-dichloroethane was treated with 0.3 mL (2.7 mmol) of 1-chloroethyl chloroformate (ACE-Cl). The resulting mixture was stirred at rt for 3 h, then at reflux for 30 min. The reaction was cooled

and concentrated. The residue was warmed to reflux in 5 mL of MeOH for 1 h. The reaction was cooled and concentrated. The crude product was used in Step C without further purification.

Step C: (R/S)- 1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl carboxylic acid, methyl ester

The title compound was prepared using an analogous procedure described in EXAMPLE I, Step E substituting (R/S)-pyrrolidin-3-yl carboxylic acid, methyl ester hydrochloride salt (from Step B) for (R/S)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester and using DIEA to neutralize the hydrochloride salt: R_F: 0.44 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.91 (t, J = 6.9, 3H), 1.30-1.35 (m, 12H), 1.60-1.66 (m, 2H), 2.13-2.17 (m, 2H), 2.54-2.69 (m, 4H), 2.80 (m, 1H), 2.99 (m, 1H), 3.09 (m, 1H), 3.66 (s, 2H), 3.72 (s, 3H), 7.16 (d, J = 8.0, 2H), 7.27 (d, J = 8.0, 2H).

Step D: (R/S)-1-(4-Nonylphenyl)methyl- 3-fluoropyrrolidin-3-yl carboxylic acid, methyl ester

To a solution of 1 mL (0.32 mmol) of 0.32M lithium diisopropylamide in THF at –78 °C was added 90 mg (0.26 mmol) of (R/S)-1-1-(4-nonylphenyl) methylbenzyl)-pyrrolidin-3-yl carboxylic acid, methyl ester (from Step C) in 1.5 mL of THF while maintaining the internal temperature at less –70 °C. After 15 min, 111 mg (0.35 mmol) of fluorobenzenesulfonimide in 0.5 mL THF was added while maintaining the internal temperature at less –68 °C. After stirring for 15 min, the reaction was warmed to 0 °C and quenched with 0.1N HCl. The reaction mixture was poured into 50 mL of Et_2O and washed with 50 mL of 1N $NaHCO_3$ and 50 mL of sat'd NaCl. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography using 19:1 v/v hexane/acetone as the eluant to afford 47 mg (50%) of the title compound as a colorless film: R_F: 0.36 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.91 (t, J = 6.8, 3H), 1.30-1.35 (m, 12H), 1.60-1.66 (m, 2H), 2.28 (m, 1H), 2.49 (m, 1H), 2.62 (t, J = 7.8, 2H), 2.69 (m, 1H), 2.95-3.10 (m, 3H), 3.69 (ABq, J = 12.8, 2H), 3.83 (s, 3H), 7.16 (d, J = 7.8, 2H), 7.27 (d, J = 7.8, 2H).

Step E: (R/S)-1-(4-Nonylphenyl)methyl-3-fluoropyrrolidin-3-yl carboxylic acid

A solution of 46 mg (0.12 mmol) of (R/S)-1-(4-nonylphenyl)methyl-3-fluoropyrrolidin-3-yl carboxylic acid, methyl ester (from Step D) in 3 mL of EtOH was treated with 0.16 mL (0.16 mmol) of 1N NaOH and stirred overnight at rt. The reaction was neutralized with 2 mL of pH 7 buffer and concentrated. Toluene was added and the resulting mixture was concentrated. The residue was purified by flash chromatography using 19:1 v/v CH_2Cl_2/MeOH, then 90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford 38 mg (86%) of the title compound as a white, waxy solid: R_F: 0.21 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz) δ 0.79 (t, J = 6.8, 3H), 1.18-1.23 (m, 12H), 1.48-1.52 (m, 2H), 2.30 (m, 1H), 2.47-2.59 (m, 3H), 3.29-3.44 (m, 3H), 3.73 (m, 1H), 3.87 (br m, 1H), 4.17 (ABq, J = 12.9, 2H), 7.12 (d, J = 7.9, 2H), 7.28 (d, J = 7.9, 2H); ESI-MS 350 (M+H); LC-1: 3.3 min.

EXAMPLE XXXVI

(R/S)-1-(4-Nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid

Step A: (R/S) 1-(4-Nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid, methyl ester

To a solution of 0.52 mL (0.52 mmol) of 1.0M sodium hexamethylsilazide in THF at –78 °C was added 153 mg (0.44 mmol) of (R/S)- 1-(4-nonylphenyl)methyl-pyrrolidin-3-yl carboxylic acid, methyl ester (from EXAMPLE XXXIV, Step C) in 1 mL of THF while maintaining the internal temperature at less –72 °C. After 20 min, 172 mg (0.65 mmol) of 2-(phenylsulfonyl)-3-phenyloxaziridine (Davis Reagent) in 1 mL of THF was added while maintaining the internal temperature at less –69 °C. After stirring for 1.25 h at –78 °C, the reaction was quenched with 1N $NaHCO_3$ and warmed to rt. After removing volatiles under reduced pressure, the reaction mixture was diluted with 50 mL of 1N $NaHCO_3$ and 50 mL of sat'd NaCl. The aqueous phase was extracted with 3X50 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography using 4:1 v/v hexane/EtOAc and 4:1 v/v hexane/acetone as the gradient to afford 11 mg (7%) of the title compound as a

colorless film: R_F: 0.39 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.90 (t, J = 6.8, 3H), 1.28-1.33 (m, 12H), 1.59-1.64 (m, 2H), 2.02 (m, 1H), 2.42 (m, 1H), 2.60 (t, J = 7.8, 2H), 2.67 (m, 1H), 2.86 (ABq, J = 10.1, 2H), 2.97 (m, 1H), 3.69 (s, 2H), 3.82 (s, 3H), 7.14 (d, J = 7.9, 2H), 7.26 (d, J = 7.9, 2H).

Step B: (R/S)- 1-(4-Nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid

The title compound was prepared using an analogous procedure described in EXAMPLE XXXIV, Step E substituting (R/S)-1-(4-nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid, methyl ester (from Step A) for (R/S)-1-(4-nonylphenyl)methyl-3-fluoropyrrolidin-3-yl carboxylic acid, methyl ester: R_F: 0.15 (90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.89 (t, J = 6.9, 3H), 1.28-1.33 (m, 12H), 1.60-1.63 (m, 2H), 2.10 (m, 1H), 2.49 (m, 1H), 2.64 (t, J = 7.7, 2H), 3.25 (m, 1H), 3.49-3.62 (m, 3H), 4.38 (ABq, J = 13.0, 2H), 7.28 (d, J = 7.8, 2H), 7.42 (d, J = 7.8, 2H); ESI-MS 348 (M+H); LC-1: 3.0 min.

EXAMPLE XXXVII

(R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl acetic acid

Step A: (R/S)- 1-(4-Nonylphenyl)methyl-pyrrolidin-3-ylacetic acid, tert-butyl ester

The title compound was prepared using an analogous procedure described in EXAMPLE I, Step E substituting (R/S)-pyrrolidin-3-yl acetic acid, tert-butyl ester hydrochloride salt for (R/S)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester and using DIEA to neutralize the hydrochloride salt: R_F: 0.53 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.90 (t, J = 6.8, 3H), 1.28-1.64 (m, 25H), 2.09 (m, 1H), 2.26-2.37 (m, 3H), 2.58-2.69 (m, 4H), 2.89 (m, 1H), 3.61-3.64 (m, 2H), 7.14 (d, J = 7.4, 2H), 7.26 (d, J = 7.4, 2H).

Step B: (R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl acetic acid

A solution of 50.5 mg (0.12 mmol) of (R/S)-1-(4-nonylphenyl)methyl-pyrrolidin-3-yl acetic acid, tert-butyl ester (from Step A) in formic acid at 55 °C was stirred for 2.25 h. Volatiles were removed under reduced pressure. The residue was purified by flash chromatography using 19:1 v/v CH_2Cl_2/MeOH, then 85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford 41 mg (94%) of the title compound as a sticky, waxy film: R_F: 0.31 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.90 (t, J = 6.9, 3H), 1.29-1.33 (m, 12H), 1.61-1.64 (m, 2H), 1.77 (m, 1H), 2.26-2.45 (m, 3H), 2.64 (t, J = 7.7, 2H), 2.71 (m, 1H), 3.08 (m, 1H), 3.23 (m, 1H), 3.38-3.44 (m, 2H), 4.28 (s, 2H), 7.28 (d, J = 8.1, 2H), 7.39 (d, J = 8.1, 2H); ESI-MS 346 (M+H); LC-1: 3.3 min.

EXAMPLE XXXVIII

(R/S)-1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-pyrrolidin-3-ylacetic acid

The title compound was prepared using procedures analogous to those described in EXAMPLE XXXVI substituting Aldehyde XVI for Aldehyde I in Step A: R_F: 0.29 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 1.77 (m, 1H), 2.26-2.46 (m, 3H), 2.71 (m, 1H), 3.07 (m, 1H), 3.23 (m, 1H), 3.37-3.34 (m, 2H), 4.28 (s, 2H), 5.38 (s, 2H), 7.13 (d, J = 8.7, 2H), 7.23 (s, 1H), 7.40-7.47 (m, 7H); ESI-MS 476 (M+H); LC-1: 3.0 min.

EXAMPLE XXXIX

(R/S)-5-[1-(4-Nonylphenyl)methylpyrrolidin-3-yl]-1*H*-tetrazole

Step A: (R/S)-1-Benzyloxycarbonyl-3-cyano pyrrolidine

The title compound was prepared using analogous procedures described in EXAMPLE XVIII (Steps A and B) substituting acrylonitrile for benzyl acrylate in Step A: R_F: 0.19 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.18-2.28 (m, 2H), 3.12 (m, 1H), 3.53 (m, 1H), 3.61-3.78 (m, 3H), 5.16 (d, J = 3.0, 2H), 7.32-7.42 (m, 5H).

Step B: (R/S)-5-[1-Benzyloxycarbonyl-pyrrolidin-3-yl]-1*H*-tetrazole

A mixture of 1.8 g (7.8 mmol) of (R/S)-1-benzyloxycarbonyl-3-cyano pyrrolidine (from Step A), 1.5 g (23 mmol) of sodium azide and 1.25 g (23 mmol) of ammonium chloride in 70 mL of DMF was stirred at 105 °C overnight. After cooling to rt, the reaction was poured into 150 mL of CH_2Cl_2 and washed with 150 mL of 1N HCl and 2X150 mL of H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified on a 40M Biotage column using 80:20:1 v/v/v CH_2Cl_2/EtOAc/HOAc as the eluant to afford 670 mg (31%) of the title compound: R_F: 0.23 (80:20:1 v/v/v CH_2Cl_2/EtOAc/HOAc); ^{1}H-NMR (500 MHz) δ 2.29, 2.48 (2m, 2H), 3.54-4.03 (m, 5H), 5.14-5.24 (m, 2H), 7.30-7.37 (m, 5H), 10.43 (br, 1H).

Step C: (R/S)-5-(Pyrrolidin-3-yl)-1*H*-tetrazole

A mixture of 662 mg (2.4 mmol) of (R/S)-5-[1-benzyloxycarbonyl-pyrrolidin-3-yl]-1*H*-tetrazole (from Step B) and 220 mg of 10% palladium on charcoal in 5 mL of MeOH was hydrogenated at atmospheric pressure using a balloon of hydrogen for 3 h. The reaction was filtered through a pad of Celite and concentrated to afford the title compound as a white solid: ^{1}H-NMR (500 MHz, CD_3OD) δ 2.27 (m, 1H), 2.49 (m, 1H), 3.39-3.51 (m, 3H), 3.70 (m, 1H), 3.85 (m, 1H).

Step D: (R/S)-5-[1-(4-Nonylbenzyl)methyl-pyrrolidin-3-yl]-1*H*-tetrazole

The title compound was prepared using an analogous procedure described in EXAMPLE XVIII, Step D substituting (R/S)-5-(pyrrolidin-3-yl)-1*H*-tetrazole (from Step C) for (R/S)-pyrrolidin-3-yl carboxylic acid: ^{1}H-NMR (500 MHz, CD_3OD) δ 0.89 (t, J = 7.0, 3H), 1.28-1.33 (m, 12H), 160.-1.63 (m, 2H), 2.33 (m, 1H), 2.55 (m, 1H), 2.64 (t, J = 7.6, 2H), 3.47-3.55 (m, 3H), 3.76 (m, 1H), 3.92 (m, 1H), 4.40 (s, 2H), 7.29 (d, J = 8.0, 2H), 7.42 (d, J = 8.0, 2H); ESI-MS 356 (M+H); LC-1: 3.3 min.

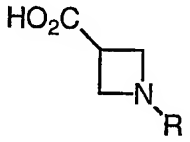
EXAMPLE XL

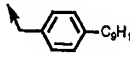
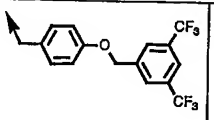
1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-3-azetidinecarboxylic acid

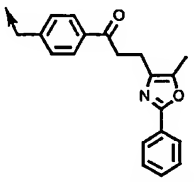
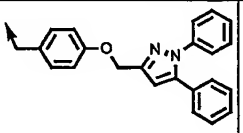
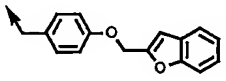
The title compound was prepared by treating a mixture of 0.12 mmol of 3-azetidinecarboxylic acid, 0.1 mmol of Aldehyde XVI, 0.007 mL (0.12 mmol) of acetic acid in 2 mL of MeOH with 10 mg (0.16 mmol) of sodium cyanoborohydride and stirring the resulting mixture at rt for 3 h. The product was purified using LC-2: ^{1}H NMR (500 MHz, CD_3OD) δ 3.34-3.37 (m, 1H), 4.08 (app s, 2H), 4.10 (app s, 2H), 4.22 (s, 2H), 4.86 (s, 2H), 5.35 (s, 2H), 7.10 (app d, J= 8.0, 2H), 7.20 (s, 1H), 7.39-7.43 (5H).

EXAMPLES XLI-XLV

EXAMPLES XLI-XLV were prepared using procedures analogous to that described in EXAMPLE XLI substituting the appropriate Aldehyde for Aldehyde XVI.

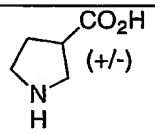
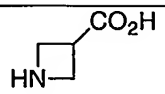
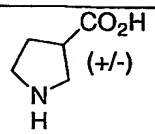


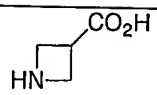
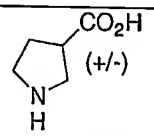
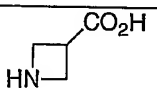
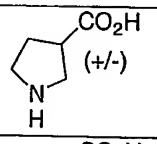
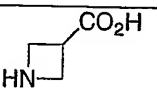
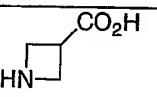
EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
XLI		LC-1	3.3	318
^{1}H-NMR (500 MHz, CD_3OD) δ 0.89 (t, J = 6.8, 3H), 1.28-1.32 (m, 12H), 1.60-1.62 (m, 2H), 2.63 (t, J = 7.7, 2H), 3.37 (m, 1H), 4.12 (s, 2H), 4.13 (s, 2H), 4.27 (s, 2H), 7.27 (d, J = 8.0, 2H), 7.35 (d, J = 8.0, 2H)				
XLII		LC-1	2.9	434
^{1}H-NMR (500 MHz, CD_3OD) δ 3.35 (m, 1H), 4.14 (s, 2H), 4.16 (s, 2H), 4.28 (s, 2H), 5.31 (s, 2H), 7.14 (d, J = 8.6, 2H), 7.42 (d, J = 8.6, 2H), 7.94 (s, 1H), 8.07 (s, 2H)				

XLIII		LC-1	2.4	405
XLIV		--	--	440
XLV		--	--	338

EXAMPLES XLVI-LIV

The following compounds were prepared by treating a mixture of 0.12 mmol of either azetidine-3-carboxylic acid or (±)-pyrroldine-3-carboxylic acid, 0.1 mmol of Aldehyde, 7 μL (0.12 mmol) of acetic acid in 2 mL of MeOH with 10 mg (0.16 mmol) of sodium cyanoborohydride and stirring the resulting mixture at rt for 1-3 h. The reaction mixtures were purified using LC-2.

EXAMPLE	Amino acid	Aldehyde #	LC-1	MS
XLVI		19	2.9 min	496 (M+H)
XLVII		19	2.9 min	482 (M+H)
XLVIII		18	3.1 min	496 (M+H)

XLIX		18	3.1 min	482 (M+H)
L		21	2.9 min	492 (M+H)
LI		21	2.9 min	478 (M+H)
LII		20	3.1 min	476 (M+H)
LIII		20	3.1 min	462 (M+H)
LIV		15	3.2 min	485 (M+H)

XAMPLE LV

(3S,4R or 3R,4S)-1-(4-Nonylbenzyl)-4-trifluoromethylpyrrolidin-3-yl carboxylic acid

Step A: 4-(Nonyl)benzylamine

4-Nonylbenzoyl chloride (6g, 20mmol) and NH_4OAc (6g,) were suspended in acetone (100mL) and stirred for 1 h at rt. Water (50mL) was added and the mixture filtered. The residue was washed with water and dried . The resulting crude amide (2.47g, ~10mmol) was dissolved in THF (5mL) and borane dimethylsulfide complex (10mL of 2M solution, 20mmol) was added dropwise, while warming to reflux. The mixture was heated for 1h. then cooled in an ice bath.

Methanol (2.5mL) was added dropwise, followed by 1N HCl in ether (11mL). The white precipitate of the HCl salt of the benzyl amine was filtered off and washed with ether. The HCl salt was taken up in 2.5N NaOH and ether and the organic layer was separated and dried over Na_2SO_4. Evaporation afforded 1.3 g of the title compound.

Step B: N-(Methoxymethyl)-N-(trimethylsilylmethyl)-(4-nonyl)benzylamine

A solution of 1.3 g (6 mmol) of 4-(nonyl)benzylamine (from Step A) and 700 mg (6 mmol) of chloromethyltrimethylsilane in 5 mL of DMSO was stirred at 90 °C for 3 h, then at rt for 16 h. The mixture was partitioned between MTBE and 1N NaOH. The organic layer was separated, washed with sat'd NaCl, dried and concentrated. Flash chromatography using 9:1 v/v hexane/EtOAc as the eluant afforded 700 mg of N-(trimethylsilylmethyl)-4-(nonyl)benzylamine.

A mixture of the crude N-(trimethylsilylmethyl)-4-(nonyl)benzylamine, 140 mg of paraformaldehyde and 15 mg of powdered NaOH in 5 mL of MeOH was stirred at 40 °C for 1 h. The mixture was diluted with ether and aged for 16 h. The mixture was concentrated and dried to afford 700 mg of the title compound: ^{1}H NMR (500 MHz, CD_3OD) δ: 7.25 (m, 2H); 7.15 (m, 2H); 4.03 (m, 2H); 3.74 (m, 2H); 3.28 (m, 2H); 2.61 (m, 2H); 2.22 (m, 2H); 1.63 (m, 4H); 1.30 (m, 14H); 0.90 (m, 3H); 0.08 (m, 9H).

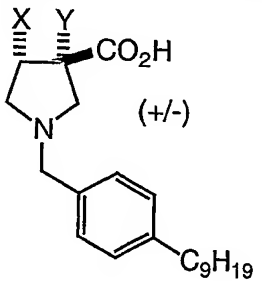
Step C: 1-(4-(Nonyl)phenyl)methyl-3-(R/S)-carboxy-4-(R/S)-trifluoromethyl pyrrolidine

A solution of 50 mg (0.14 mmol) of N-(methoxymethyl)-N-(trimethylsilylmethyl)-(4-nonyl)benzylamine (from Step B) and 20 mg (0.14 mmol) of *trans*-4,4,4-trifluoro-2-butenoic acid (0.137mmol) in 1 mL of CH_2Cl_2 was treated with 1 drop of TFA and the resulting mixture was heated at 35 °C for 1h. The reaction was cooled, concentrated then and then purified using LC-2 to afford the title compound: ^{1}H NMR (500 MHz, CD_3OD) δ 7.25 (d, J = 8, 2H); 7.19 (d, J = 8, 2H);

3.87 (m, 2H); 3.54 (m, 1H); 3.27(m, 4H); 2.93 (m, 1H); 2.61 (m, 2H); 1.62 (m, 2H); 1.30 (m, 14H); 0.90 (t, J = 6.7, 3H); ESI-MS 400.3 (M+H).

EXAMPLES LVI-LVIII

EXAMPLES LVI-LVIII were prepared using procedures analogous to those described in EXAMPLE LV substituting the appropriate α,β-unsaturated acid in Step C.

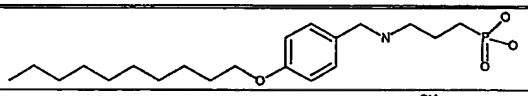
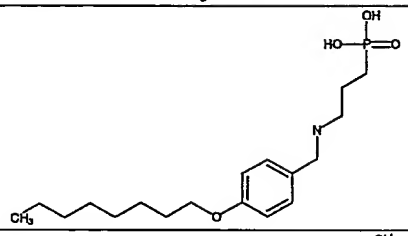
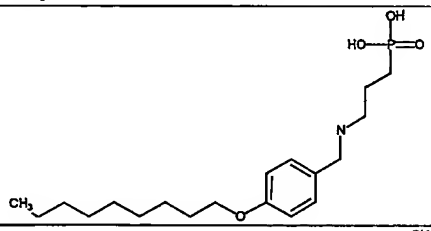
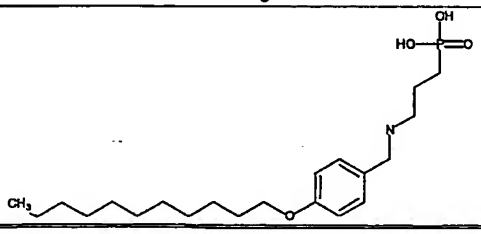


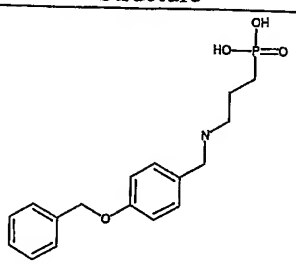
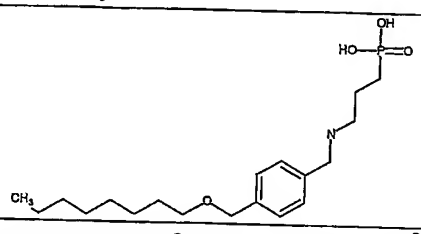
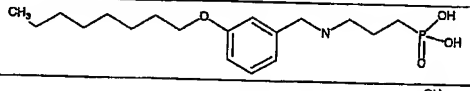
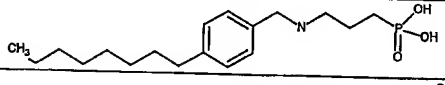
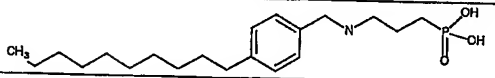
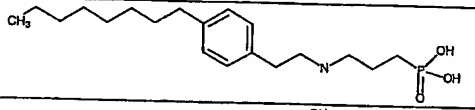
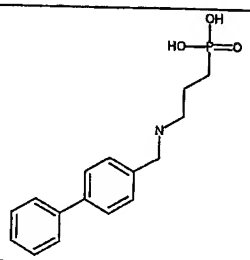
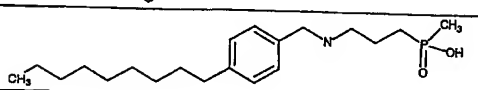
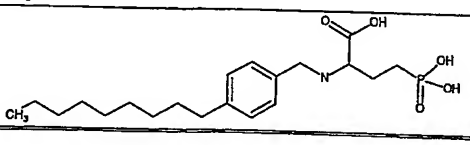
EXAMPLE #	X	Y	ESI-MS (M+H)
LVI	H	CF_3	400.3
^1H NMR (500 MHz, CD_3OD) δ: 7.43 (d, J = 8 Hz, 2H); 7.29 (d, J = 8 Hz 2H); 4.35 (s, 2H); 4.04 (d, J = 12Hz, 1H); 3.46 (m, 1H); 2.65 (m, 3H); 2.42 (m, 1H); 1.62 (m, 2H); 1.30 (m, 14H); 0.90 (t, J = 6.7 3H)			
LVII	CO_2H	H	375.3
^1H NMR (500 MHz, CD_3OD) δ: 7.35 (m, , 4H); 4.4 (m, 1H); 4.12 (m, 2H); 3.64 (m, 1H); 2.69 (m, 5H); 1.64 (m, 1H); 1.30 (m, 14H); 0.90 (m, 3H)			
LVIII	H	CH_2CO_2H	390.3

^{1}H NMR (500 MHz, CD_3OD) δ: 7.36 (m, , 4H); 4.43 (m, , 1H); 4.14 (m, 3H); 3.79 (m, 1H); 3.50 (m, 1H); 3.09 (m, 2H); 2.70 (m, 8H); 3.18 (m, 1H); 2.65 (m, 2H); 2.3 (m, 2H); 1.61 (m, 2H); 1.29 (M, 14H); 0.89 (m, 3H)

METHODS FOR PREPARING N-(BENZYL)AMINOALKYLCARBOXYLATES, PHOSPHINATES AND PHOSPONATES

The structures of Examples 1-150 are shown in the following table:

Example Number	Structure
1	
2	
3	
4	

Example Number	Structure
5	
6	
7	
8	
9	
10	
11	
12	
13	

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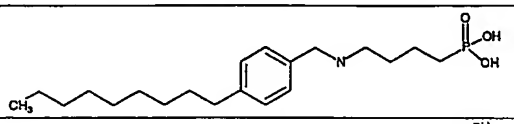
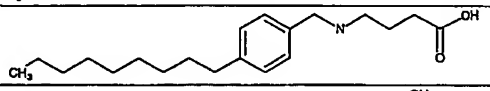
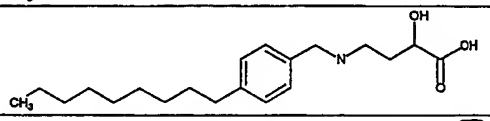
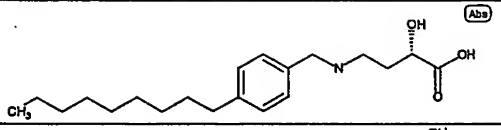
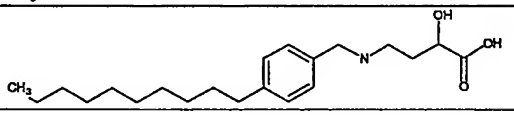
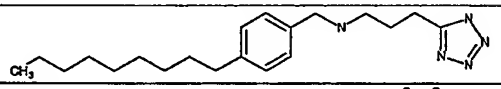
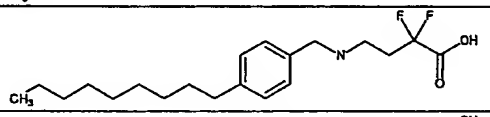
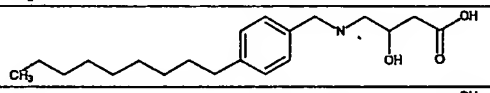
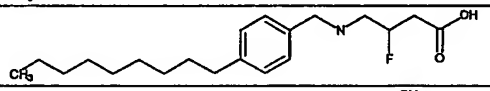
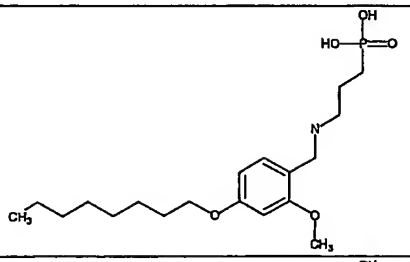
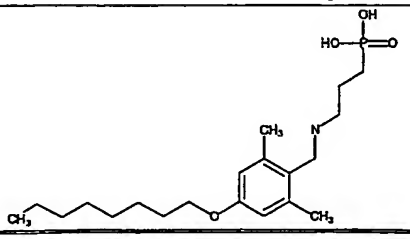
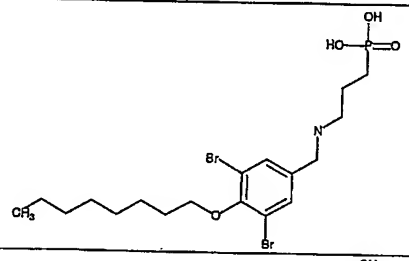
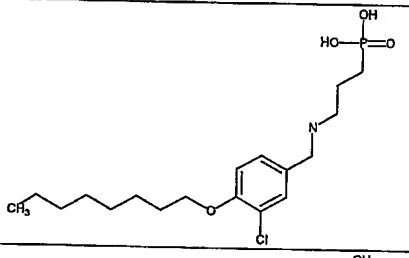
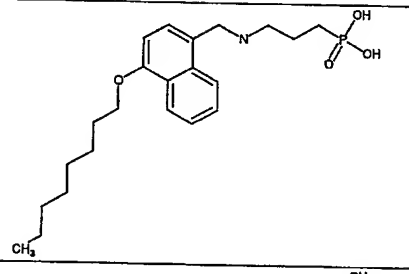
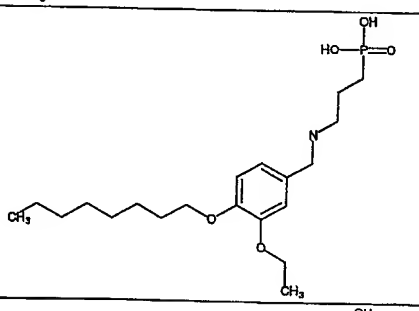
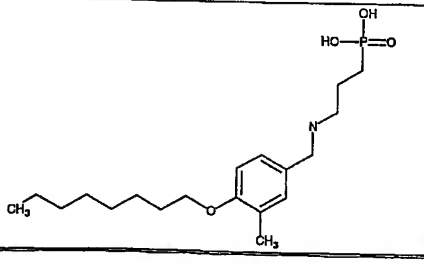
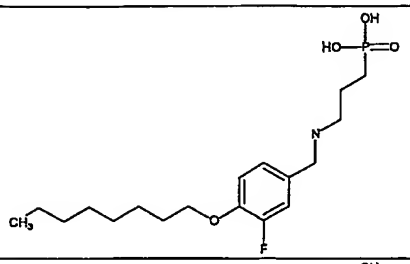
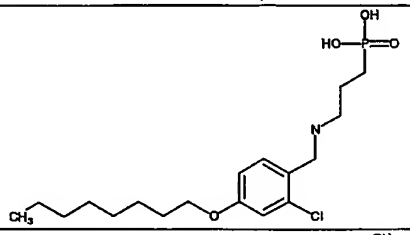
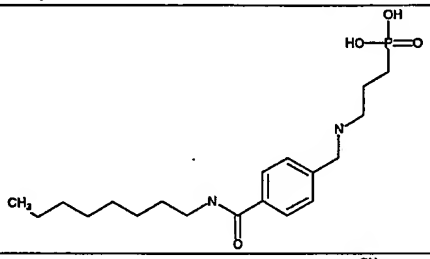
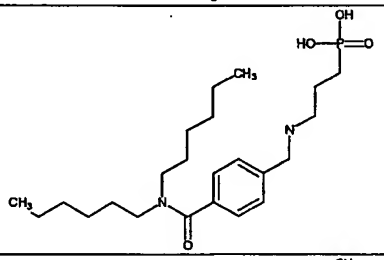
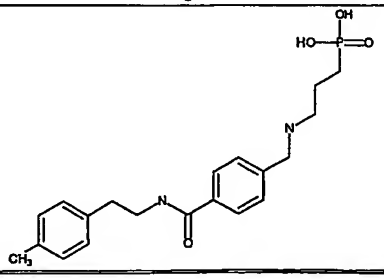
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	

Example Number	Structure
25	
26	
27	
28	
29	

Example Number	Structure
30	
31	
32	
33	
34	

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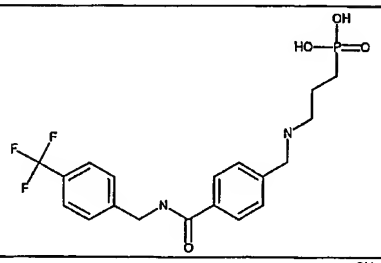
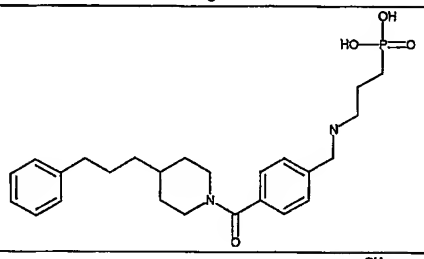
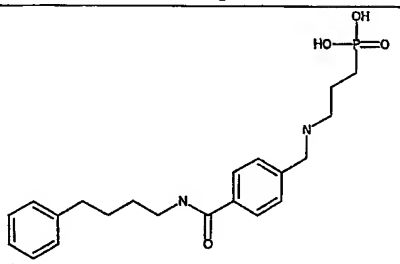
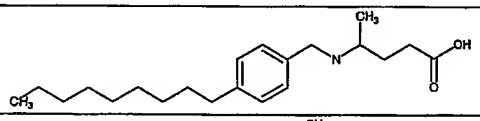
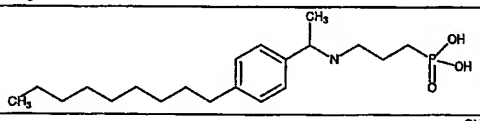
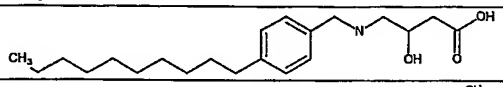
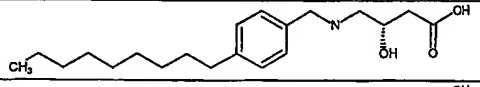
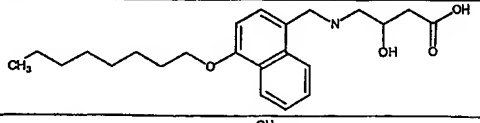
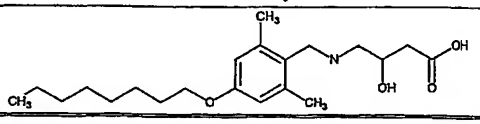
35	
36	
37	
38	
39	
40	
41	
43	
44	

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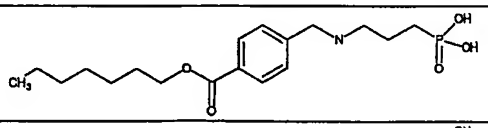
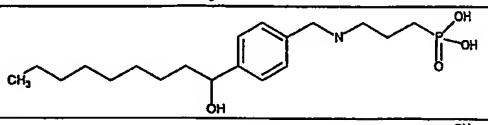
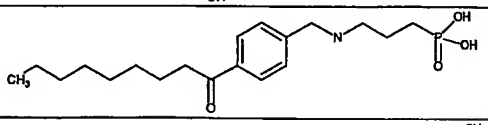
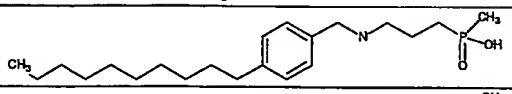
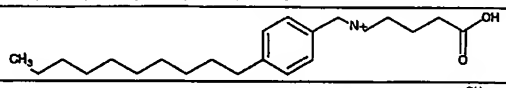
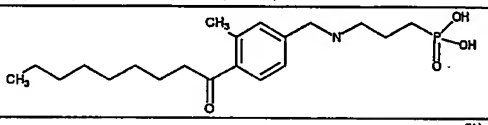
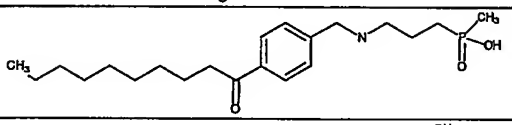
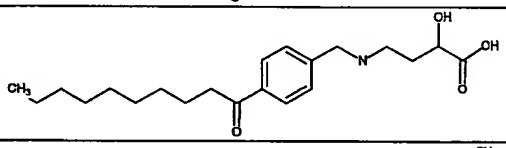
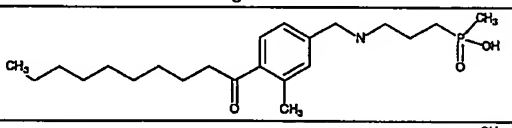
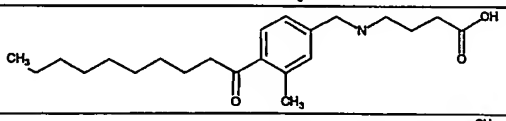
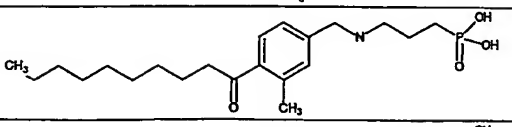
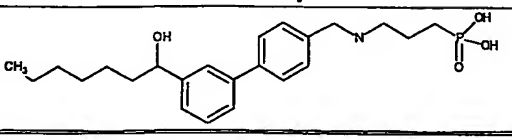
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	

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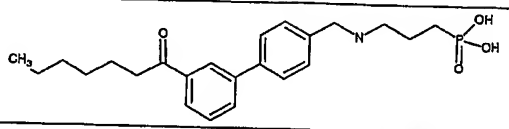
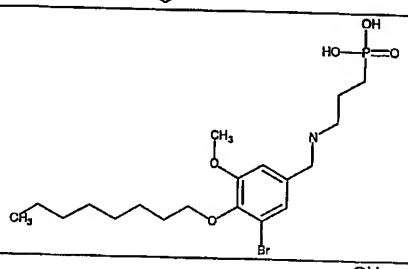
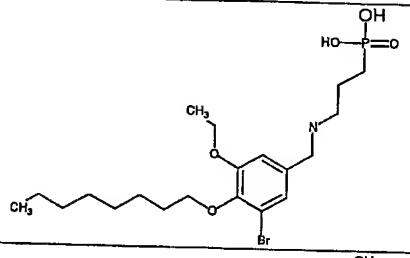
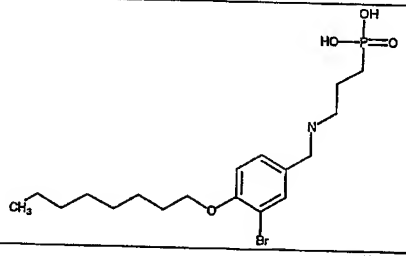
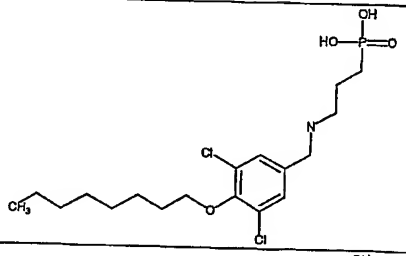
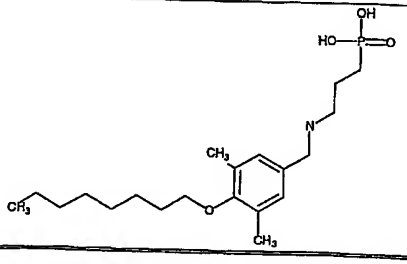
57	
58	
59	
60	
61	
62	

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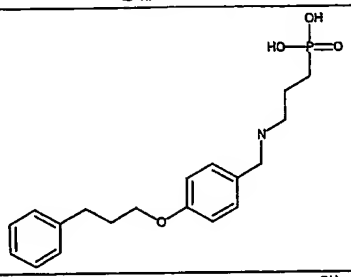
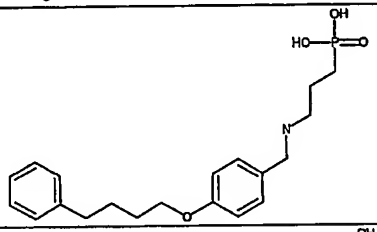
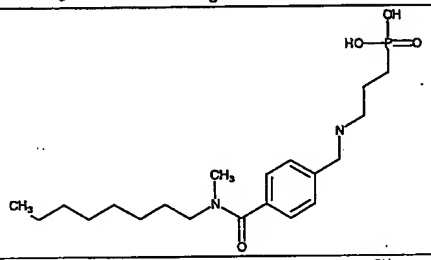
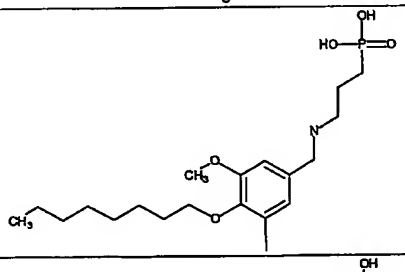
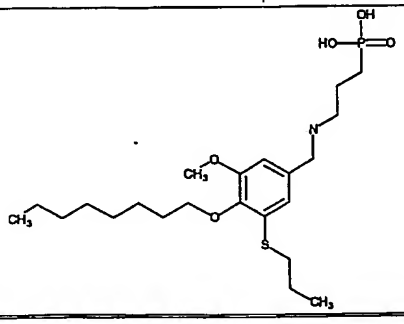
63	
64	
65	
66	
67	

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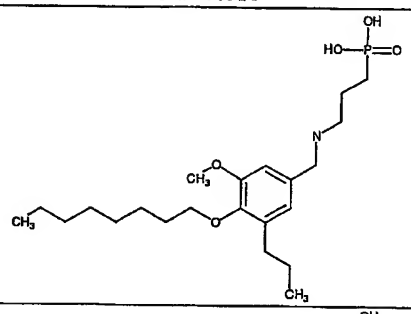
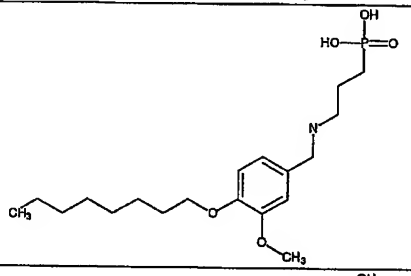
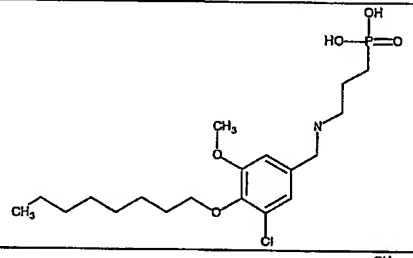
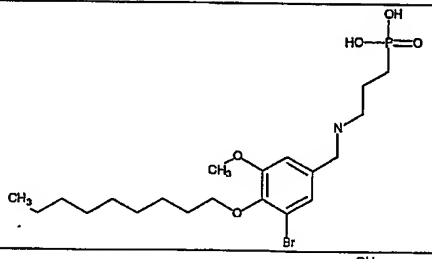
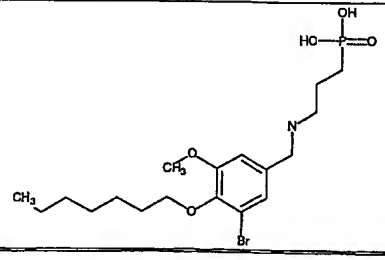
68	
69	
70	
71	
72	

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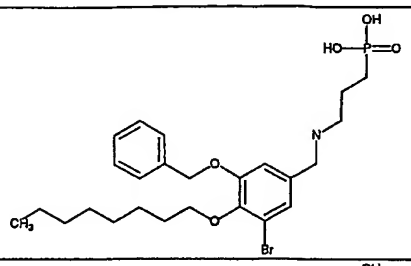
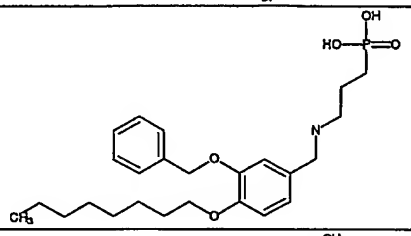
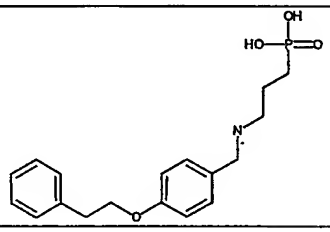
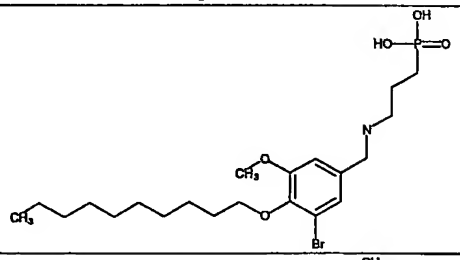
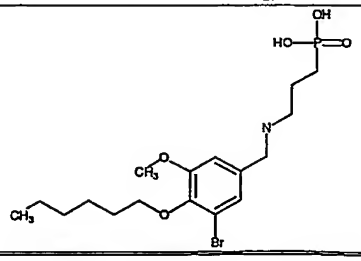
73	
74	
75	
76	
77	

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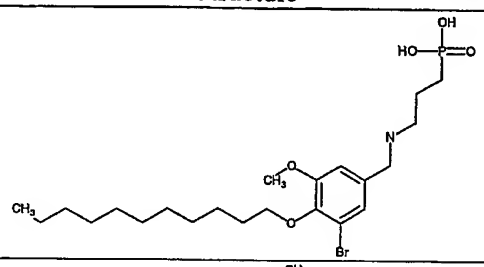
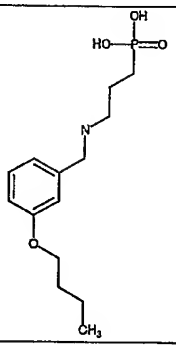
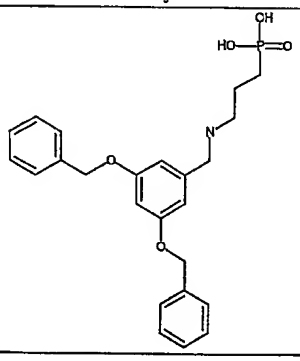
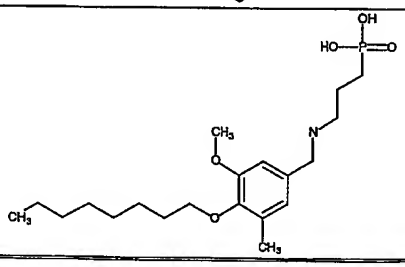
78	
79	
80	
81	

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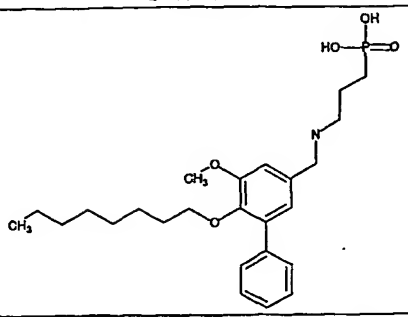
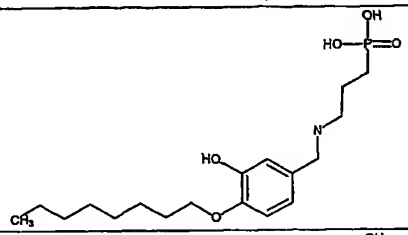
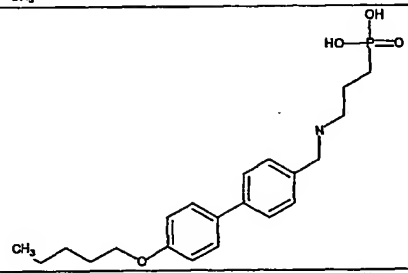
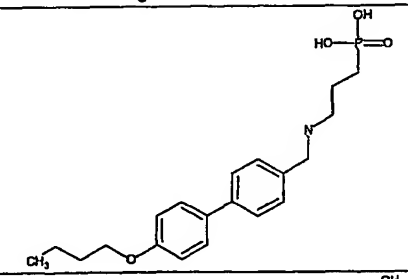
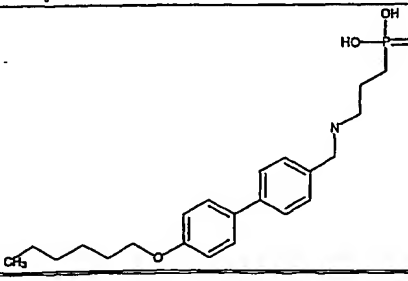
82	
83	
84	
85	
86	

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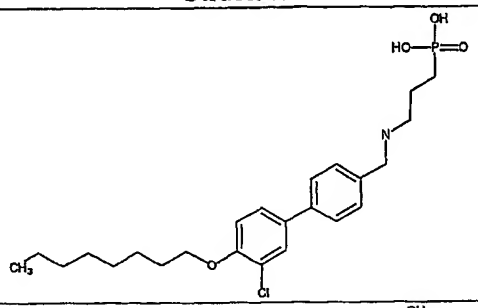
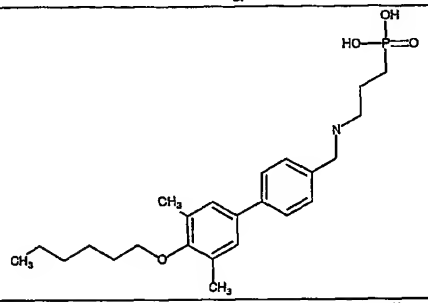
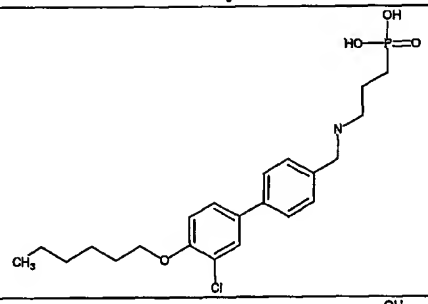
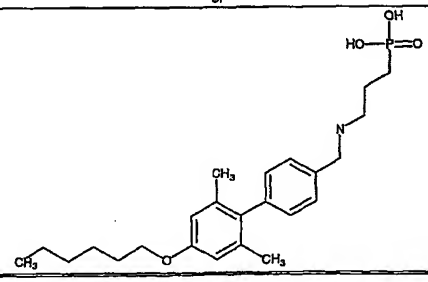
87	
88	
89	
90	

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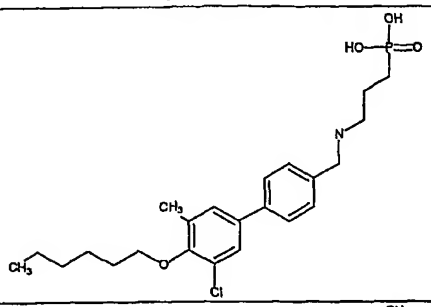
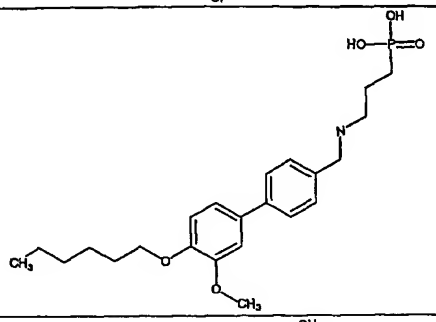
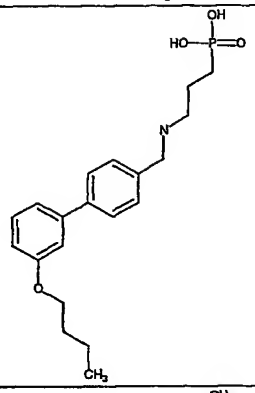
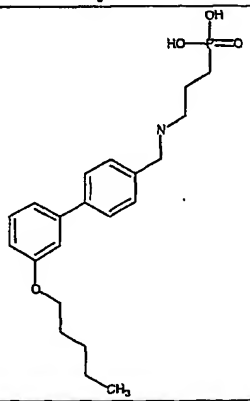
91	
92	
93	
94	

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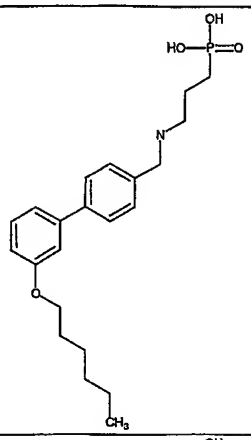
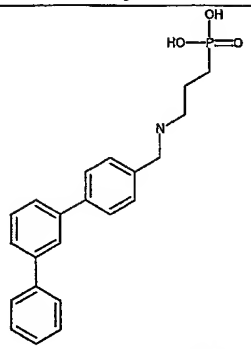
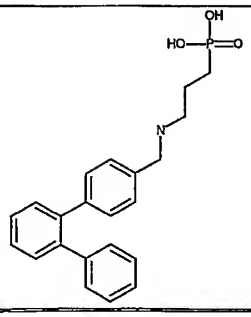
95	
96	
97	

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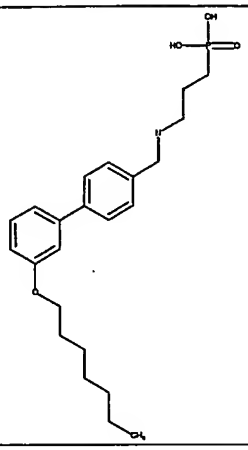
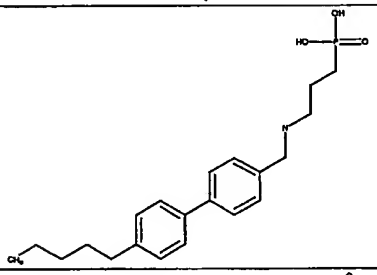
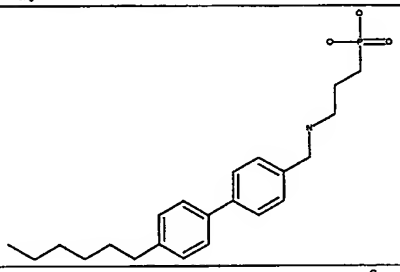
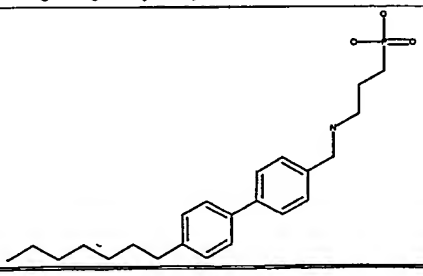
98	
99	
100	
101	

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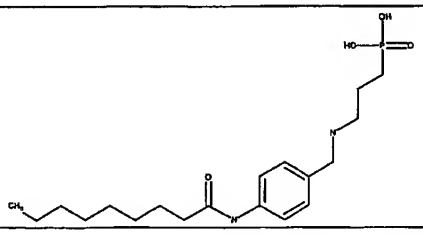
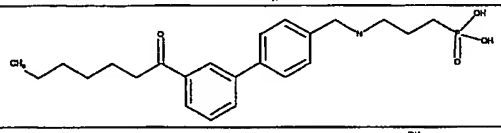
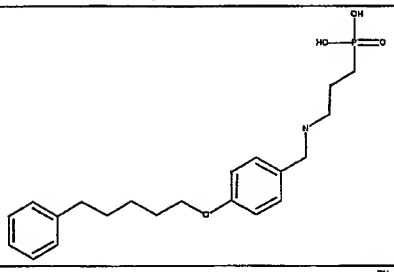
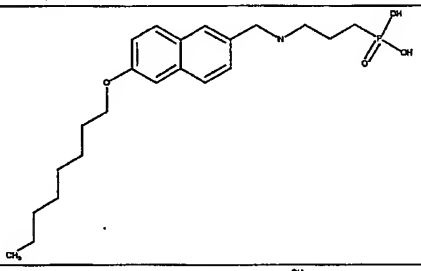
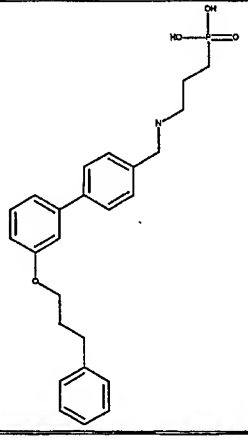
102	
103	
104	
105	
106	

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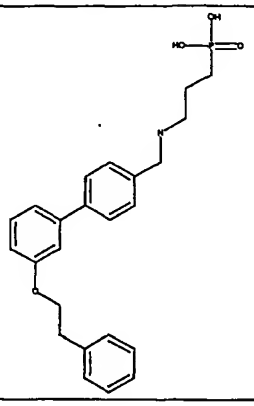
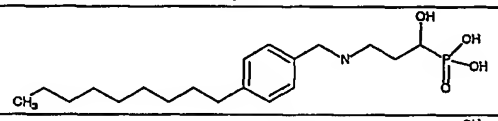
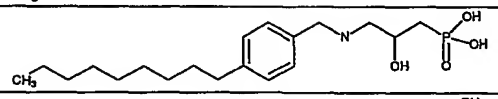
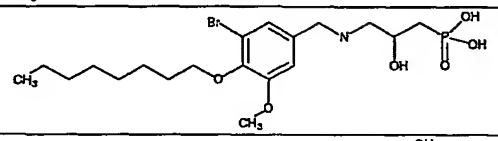
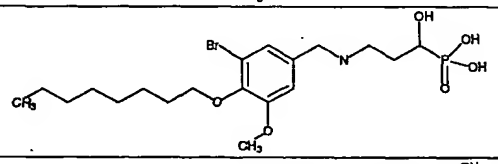
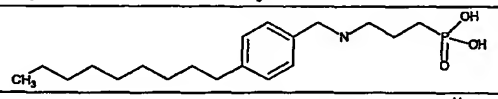
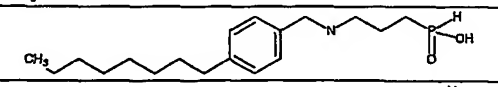
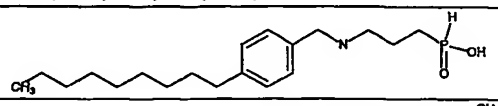
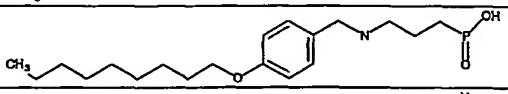
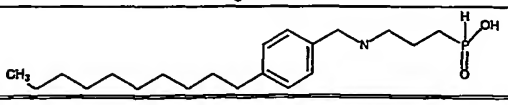
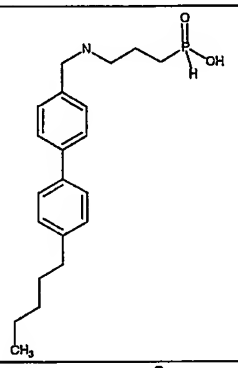
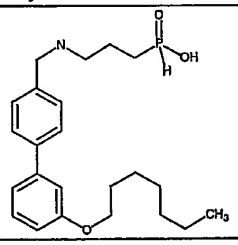
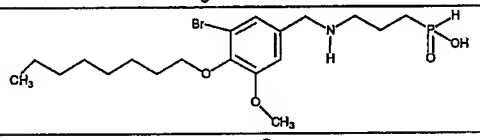
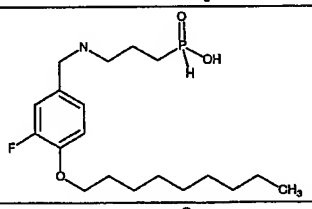
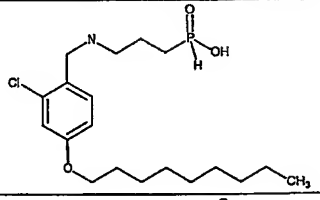
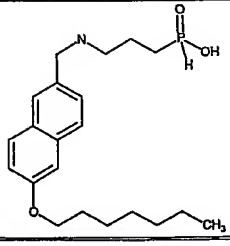
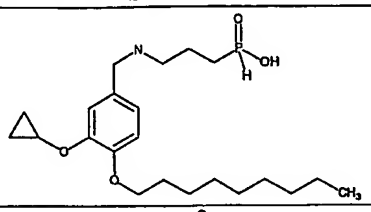
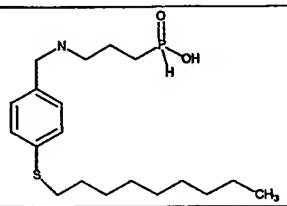
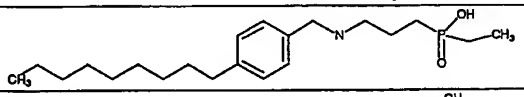
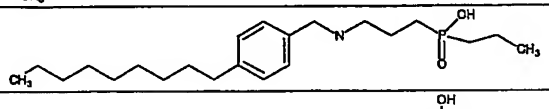
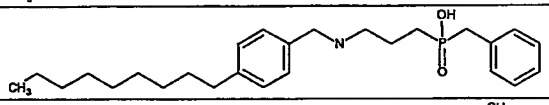
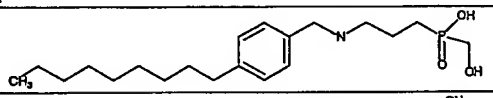
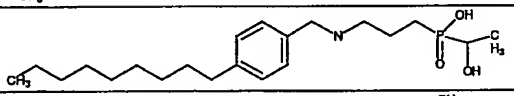
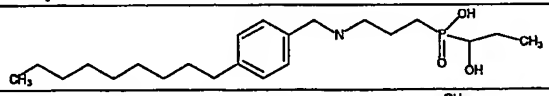
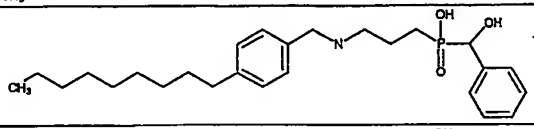
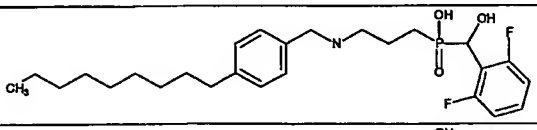
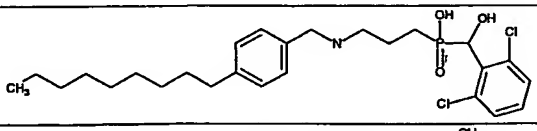
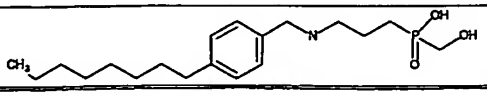
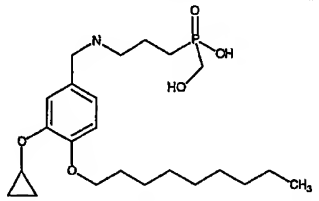
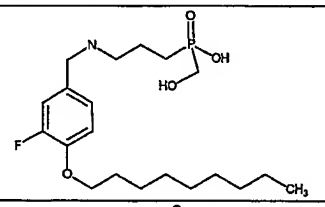
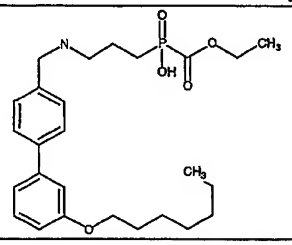
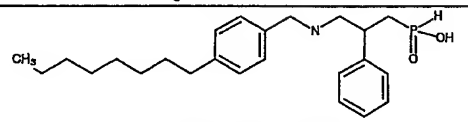
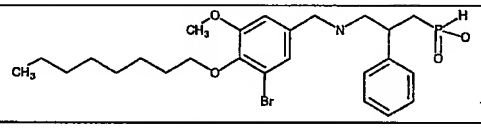
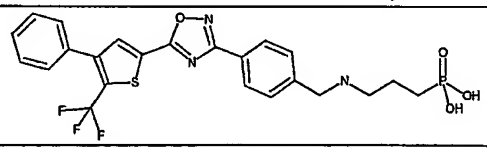
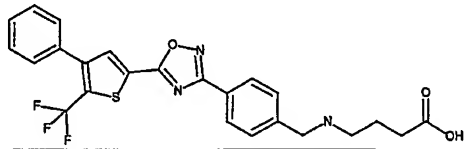
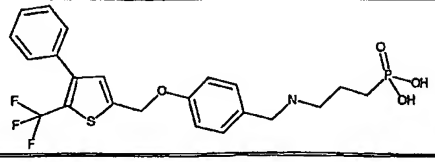
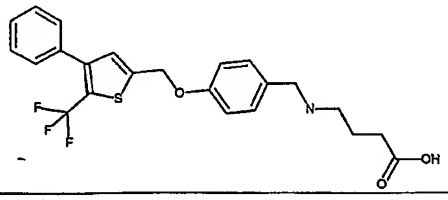
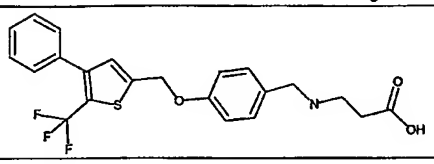
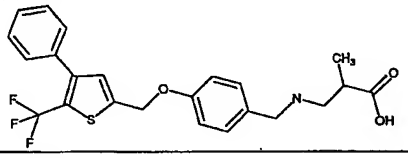
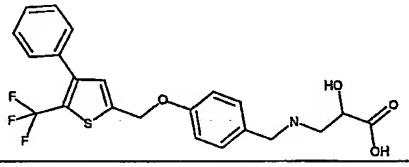
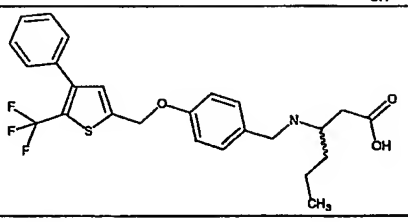
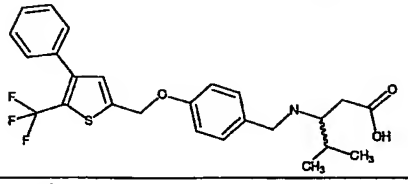
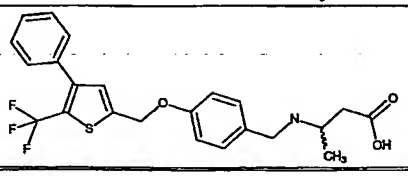
107	
108	
109	
110	
111	
112	
113	
114	
115	
116	

Example Number	Structure
117	
118	
119	
120	
121	
122	

Example Number	Structure
123	
124	
125	
126	
127	
128	
129	
130	
131	
132	
133	
134	

Example Number	Structure
135	
136	
137	
138	
139	
140	
141	
142	

Example Number	Structure
143	
144	
145	
146	
147	
148	
149	

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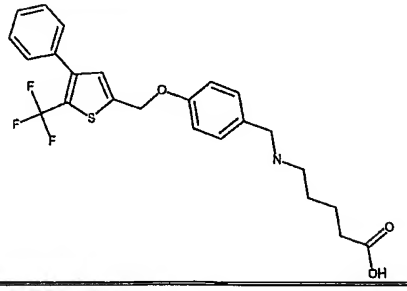
150	

GENERAL METHODS

Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Conventional flash chromatography was carried out on silica gel (230-400 mesh). Flash chromatography was also carried out using a Biotage Flash Chromatography apparatus (Dyax Corp.) on silica gel (32-63 mM, 60 Å pore size) in pre-packed cartridges of the size noted. NMR spectra were obtained in $CDCl_3$ unless otherwise noted. Coupling constants (J) are in hertz (Hz). Abbreviations: diethyl ether (ether), triethylamine (TEA), N,N-diisopropylethylamine (DIEA), tetrahydrofuran (THF), saturated (sat'd), room temperature (rt), hour(s) (h or hr), min(s) (min). For all tables that follow any NMR data follows the compound.

HPLC METHODS

LC-1: Waters Xterra MS C18, 5 μ, 4.6 x 50 mm column, 10:90 to 95:5 v/v CH_3CN/H_2O + 0.05% TFA over 4.5 min, hold 1 min, PDA detection 200-600 nm, flow rate = 2.5 mL/min.

LC-2: Analytical Sales and Service Armor C8 5 μ 20 x 100 mm column, 10:90 to 90:10 v/v CH_3CN/H_2O + 0.05% TFA over 12 min, hold 4 min, UV detection at either 210, 220 or 254 nM, flow rate = 10 mL/min.

LC-3: YMC-Pack Pro C18, 5μ, 20 mm x 150 mm column, gradient 10:90-80:20 v/v $CH_3CN:H_2O$ + 0.1% TFA over 23 min then hold at 100:0 v/v $CH_3CN:H_2O$ + 0.1% TFA for 7 min; 20 mL/min, 254 nm.

PREPARATION OF ALDEHYDE INTERMEDIATES

Aldehyde 1

4-Octyloxybenzaldehyde

4-Hydroxybenzaldehyde (1.00 g, 0.82 mmol), potassium carbonate (1.70 g, 12.28 mmol) and 1-iodooctane (2.16 g, 9.00 mmol) were heated together in acetonitrile at 80°C for 16 h. The reaction was cooled, filtered and concentrated. Silica gel chromatography eluting with hexane/ethyl acetate (20:1) gave a colorless oil (1.63 g): ^{1}H NMR (500 MHz) δ 9.99 (s, 1H), 7.44-7.46 (m, 2H), 7.40 (s, 1H), 7.19 (m, 1H), 4.01 (t, J=6.6 Hz, 2H), 1.80 (m, 2H), 1.42-1.50 (m, 2H), 1.24-1.39 (m, 8H), 0.89 (t, J=6.9 Hz, 3H).

Aldehyde 2

4-Hydroxy-3-propyloxybenzaldehyde

3,4-Dihydroxybenzaldehyde (0.5 g, 3.62 mmol) was dissolved in DMF (10 mL) and sodium hydride (0.087 g, 3.62 mmol) was added. The reaction mixture was stirred at rt for 10 min. Iodopropane (0.35 mL, 0.62 mmol) was added and the reaction was stirred at 80 °C for 2.5 h. The reaction was diluted with ethyl acetate and washed with 2N HCl and water. Silica gel chromatography eluting with 35% ethyl acetate/hexane yielded 0.16 g of desired product: ESI-MS 181 (M+H).

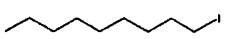
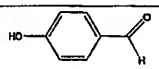
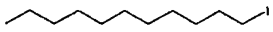
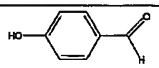
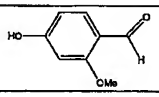
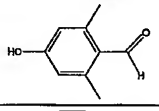
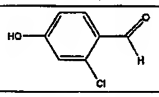
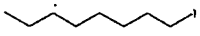
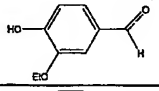
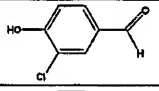
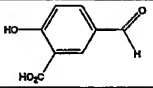
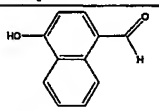
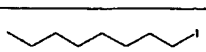
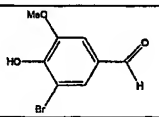
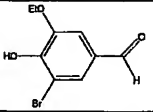
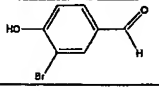
Aldehyde 3

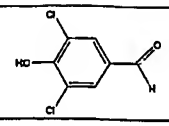
6-Hydroxy-2-naphthaldehyde

Aluminum trichloride (1.07 g, 8.06 mmol) was added to a solution of 6-methoxy-2-naphthaldehyde (1.0 g, 5.37 mmol) in chlorobenzene (15 mL). The reaction mixture was stirred at 130 °C for 4 h. The reaction was quenched with water (5 mL) and conc. HCl (2 mL). The reaction mixture was dissolved in ethyl acetate and washed with water and brine and dried over anhydrous magnesium sulfate. Silica gel chromatography eluting with 10% ethyl acetate/hexane yielded 0.35 g of desired product: ESI-MS173.0 (M+H).

Aldehydes 4-34

The following Aldehydes (4-34) were prepared using a procedure analogous to that described for Aldehyde 1 substituting A for 1-iodooctane and B for 4-hydroxybenzaldehyde.

Aldehyde	A	B	ESI-MS
4			249.3
5			277.1
6			265.4
7			263.1
8			269.0
9			279.1
10			
11			262.0
12			
13			343.0
14			357.1
15			

16			
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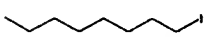
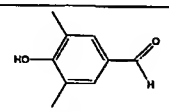
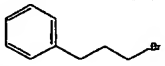
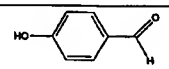
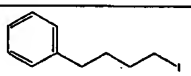
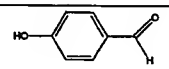
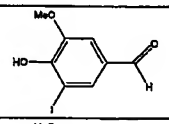
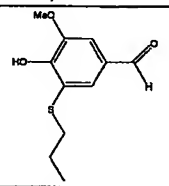
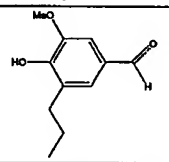
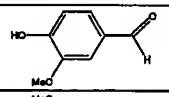
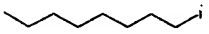
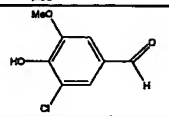
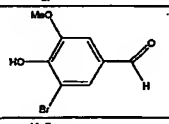
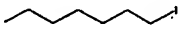
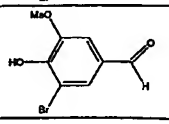
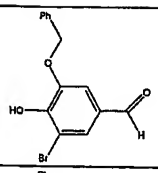
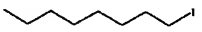
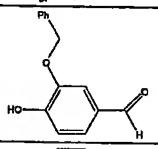
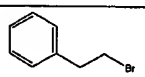
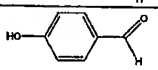
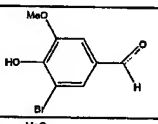
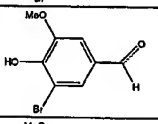
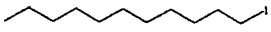
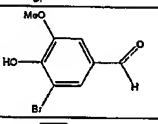
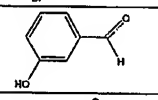
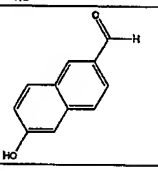
17			
18			241.1
19			255.2
20			391.1
21			339.3
22			307.3
23			265.2
24			299.1
25			357.1
26			329.0

27			419.1
28			341.3
29			227.1
30			370.9
31			317.1
32			382.7
33			179.1
34			285.1

Aldehyde 35

3-Methoxy-5-methyl-4-octyloxybenzaldehyde

Aldehyde 20 (0.20 g, 0.51 mmol) and tetramethyl tin (0.2 g, 1.12 mmol) were dissolved in N-methyl pyrrolidinone (1 mL) in a sealed tube. Palladium tetrakis(triphenylphosphine) (0.016 g, 0.014 mmol) and copper iodide (0.01 g, 0.05 mmol) were added to the reaction mixture which was heated at 65° for 16 h. The reaction mixture was diluted with ethyl acetate and washed with 2N HCl, brine and was dried over magnesium sulfate. Silica gel chromatography eluting with 10% ethyl acetate/hexane gave desired product: ESI-MS 279.2 (M+H).

Aldehyde 36

3-Methoxy-5-phenyl-4-octyloxybenzaldehyde

Aldehyde 20 (0.25 g, 0.64 mmol), phenylboronic acid (0.12 g, 0.96 mmol), potassium carbonate (0.27 g, 1.92 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.15 g, 0.016 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.022 g, 0.064 mmol) were dissolved in tetrahydrofuran (1 mL). The reaction mixture was stirred at rt for 3 h then at 50 °C for 16 h. The reaction mixture was filtered through celite. Silica gel chromatography eluting with 10% ethyl acetate/hexane gave desired product: ESI-MS 341.2 (M+H).

Aldehyde 37

3-Hydroxy-4-octyloxybenzaldehyde

Aldehyde 28 (0.25 g, 0.77 mmol) was dissolved in methylene chloride (4 mL) and boron tribromide dimethylsulfide complex (0.6 g, 1.93 mmol) was added dropwise. The reaction mixture was stirred at rt for 1 h. The reaction was quenched with methanol and concentrated *in vacuo*. Silica gel chromatography eluting with 10% ethyl acetate/hexane yielded 0.155 g of desired product: ESI-MS 251.2 (M+H).

Aldehyde 38

4-(Nonoylamido)benzaldehyde

4-Aminobenzaldehyde (0.3 g, 2.5 mmol) was dissolved in methylene chloride (8 mL) and nonanoyl chloride (0.5 mL, 2.7 mmol) was added followed by DIEA (1.14 mL, 6.25 mmol). The reaction was stirred at rt for 3 h. Silica gel chromatography eluting with 25% ethyl acetate/hexane yielded impure product Further purified by HPLC to give 30.0 mg of desired product: ESI-MS 262.0 (M+H).

Aldehyde 39

4-(5-Phenylpentyloxy)benzaldehyde

Diethylazodicarboxylate (0.49 g, 2.8 mmol) in tetrahydrofuran (2 mL) was added to a solution of 4-hydroxybenzaldehyde (0.25 g, 2.05 mmol), 5-phenyl-1-pentanol (0.34 mL, 2.05 mmol) and triphenylphosphine (0.73 g, 2.80 mmol) in tetrahydrofuran (10 mL) at rt. The reaction was stirred for 2h. The reaction mixture

was concentrated *in vacuo*. Silica gel chromatography eluting with 20% ethyl acetate/hexane yielded 0.070 g of desired product: ^{1}H NMR (500 MHz , CD_3OD): δ 9.83 (s, 1H), 7.86 (d, J=8.7 Hz, 2H), 7.25 (t, 2H), 7.14-7.20 (m, 3H), 7.06 (d, J=8.7 Hz, 2H), 4.09 (t, J=6.4 Hz, 2H), 2.65 (t, J=7.7 Hz, 2H), 1.80-1.88 (m, 2H), 1.68-1.75 (m, 2H), 1.49-1.57 (m, 2H).

Aldehyde 40

3'-Chloro-4'-octyloxy-4-biphenylbenzaldehyde

Step A: 1-Bromo-3-chloro-4-octyloxybenzene

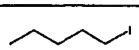
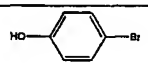
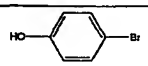
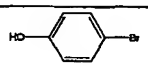
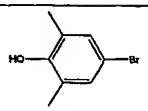
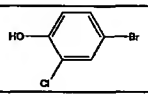
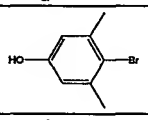
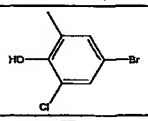
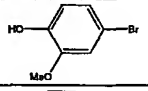
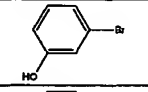
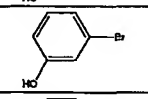
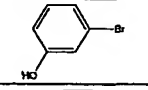
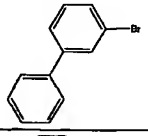
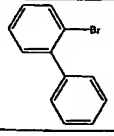
1-Bromo-3-chloro-4-hydroxybenzene (0.50 g, 2.41 mmol) was dissolved in acetonitrile (20 mL) and stirred at rt. Potassium carbonate (0.47 g, 3.37 mmol) and iodooctane (0.57 mL, 3.13 mmol) were added and the reaction was heated to 80 °C for 4 h. The reaction was diluted with ethyl acetate, washed with water and dried over anhydrous magnesium sulfate. Silica gel chromatography eluting with 1% ethyl acetate/hexane yielded 0.6 g of product: ESI-MS 317.0 (M+H).

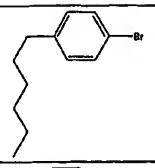
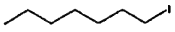
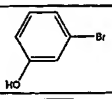
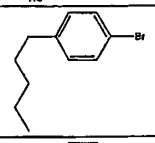
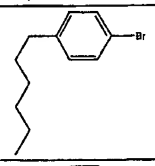
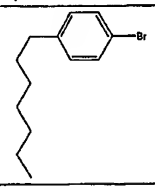
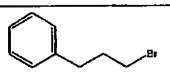
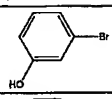
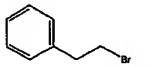
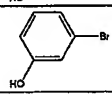
Step B: 3'-Chloro-4'-octyloxy-4-biphenylbenzaldehyde

Palladium acetate (0.005 g, 0.022 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.015 g, 0.044 mmol) were added to a solution of (4-formylphenyl)boronic acid (0.25 g, 1.65 mmol), 1-bromo-3-chloro-4-octoxybenzene (0.35 g, 1.10 mmol, from Step A), and potassium fluoride (0.19 g, 3.30 mmol) in 1,4-dioxane (3 mL). The reaction mixture was heated at 75 °C for 3 h. The reaction was cooled, filtered through celite and concentrated *in vacuo*. Silica gel chromatography eluting with 1% ethyl acetate/hexane yielded 0.17 g of desired product: ^{1}H NMR (500 MHz , CD_3OD): δ 10.01 (s, 1H), 7.97 (d, J=8.0 Hz, 2H), 7.80 (d, J=8.0 Hz, 2H), 7.74 (s, 1H), 7.61 (d, J=7.7 Hz, 1H), 7.16 (d, J=8.7 Hz, 1H) 4.11 (t, J=6.2 Hz, 2H), 1.80-1.89 (m, 2H), 1.50-1.60 (m, 2H), 1.28-1.46 (m, 8H), 0.88-0.97 (m, 3H)

Aldehydes 41-60

The following Aldehydes (41-60) were made using procedures analogous to those described for Aldehyde 40 substituting A for 1-iodooctane and B for 1-bromo-3-chloro-4-hydroxybenzene in Step A

Aldehyde	A	B	ESI-MS
41			269.1
42			255.0
43			283.1
44			311.0
45			
46			311.3
47			331.1
48			313.2
49			255.1
50			269.2
51			
52	N/A		259.0
53	N/A		259.0

54	N/A		267.1
55			297.1
56	N/A		253.2
57	N/A		267.1
58	N/A		
59			
60			

Aldehyde 61

4-(Octyloxymethyl)benzaldehyde

Step A: 4-(Octyloxymethyl)benzyl alcohol

Sodium hydride (0.17 g, 7.20 mmol) was added to a solution of 1,4-benzene dimethanol (1.00 g, 7.20 mmol) in THF at 0 °C. The reaction was stirred for 1 h. 1-iodooctane (1.73 g; 7.20 mmol) was added and the reaction mixture was warmed to rt for 4 h and then heated at 50°C for 2 days. The reaction was cooled and filtered. Silica gel chromatography eluting with 15% ethyl acetate/hexane gave 0.14 g of product: ^{1}H NMR (500 MHz) δ 7.34-7.40 (m, 4H), 4.68-4.72 (m, 2H), 4.51 (s, 2H), 3.46-3.50 (m, 2H), 1.61-1.68 (m, 2H), 1.24-1.40 (m, 10H), 0.88-0.92 (m, 3H).

Step B: 4-(Octyloxymethyl)benzaldehyde

4-(Octyloxymethyl)benzyl alcohol (0.14 g, 0.56 mmol, from Step A) was dissolved in methylene chloride (1.5 mL) and the reaction mixture was cooled to 0 °C. 4-methylmorpholine N-oxide (0.10 g, 0.84 mmol) and molecular sieves (4A) (0.25 g) were added. Tetrapropylammonium perruthenate (0.004 g, 0.011 mmol) was added and the resulting mixture was stirred for 1 h. The reaction mixture was filtered through celite. Silica gel chromatography eluting with 6% ethyl acetate/hexane gave 0.018 g of product: ^{1}H NMR (500 MHz) δ 10.02 (s, 1H), 7.86-7.90 (m, 2H), 7.50-7.55 (m, 2H), 4.58-4.62 (s, 2H), 3.50-3.55 (m, 2H), 1.62-1.70 (m, 2H), 1.24-1.35 (m, 2H), 0.87-0.93 (m, 2H).

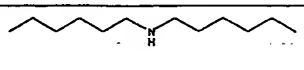
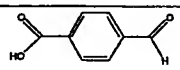
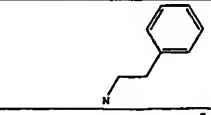
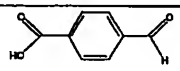
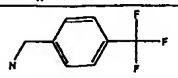
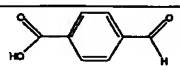
Aldehyde 62

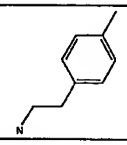
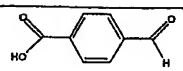
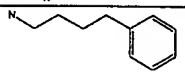
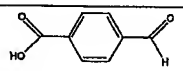
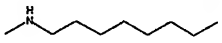
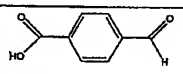
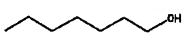
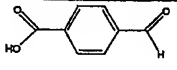
4-(N-Octylcarboxamido)benzaldehyde

DIEA (0.43 mL, 2.33 mmol) was added to a solution of 4-carboxybenzaldehyde (0.23 g, 1.55 mmol), octylamine (0.20 g, 1.55 mmol) and PyBoP (0.89 g, 1.71 mmol) in methylene chloride (2.5 mL). The reaction was stirred at rt for 16 h after which it was concentrated. Silica gel chromatography eluting with 25% ethyl acetate/hexane gave 0.30 g of product: ESI-MS 262.1 (M+H).

Aldehydes 63-73

The following Aldehydes (63-73) were made using a procedure analogous to that described for Aldehyde 62 substituting A for octylamine.

Aldehyde	A	B	ESI-MS
63			318.2
64			253.0
65			

66			282.2
67			282.2
68			
69			
^{1}H NMR (500 MHz): δ 10.10 (s, 1H), 8.20 (d, J=8.2 Hz, 2H), 7.95 (d, J=8.2 Hz, 2H), 4.35 (t, J=6.8 Hz, 2H), 1.75-1.85 (m, 2H), 1.40-1.50 (m, 2H), 1.25-1.40 (m, 6H), 0.89 (t, J=7.0 Hz, 3H).			

Aldehyde 70

4-(1-Hydroxynon-1-yl)benzaldehyde

Terephthaldicarboxaldehyde (2.00 g, 14.91 mmol) was dissolved in tetrahydrofuran (25 mL) and cooled to 0°C. Octylmagnesium chloride (7.5 mL, 2.0M in THF, 15 mmol) was added dropwise. After 15 min, the reaction was quenched with 2N aqueous hydrochloric acid (50 mL) and diluted with ethyl acetate (50 mL). The organic layer was separated, washed with sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 9% ethyl acetate/hexane gave 0.19 g (0.77 mmol, 5.1%) of product: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.87 (d, J=8.0 Hz, 2H), 7.52 (d, J=8.3 Hz, 2H), 4.75-4.80 (m, 1H), 1.68-1.82 (m, 2H), 1.22-1.45 (m, 12H), 0.91 (t, J=7.0 Hz, 3H).

Aldehyde 71

4-(1-Nonoyl)benzaldehyde

Dess-Martin periodinane (0.268 g, 0.632 mmol) was added to a solution of Aldehyde 70 (0.125 g, 0.505 mmol) in methylene chloride (3.0 mL). After 1 h, the reaction was filtered and concentrated in vacuo. Silica gel chromatography eluting with 5% ethyl acetate/hexane gave 0.107 g (0.446 mmol, 88%) of product: ^{1}H NMR (500 MHz) δ 10.1 (s, 1H), 8.10 (d, J=8.2 Hz, 2H), 7.97 (d, J=8.2 Hz, 2H), 3.00 (t, J= 7.3 Hz, 2H), 1.70-1.8 (m, 2H), 1.22-1.42 (m, 10H), 0.88 (t, J=7.0 Hz, 3H).

Aldehyde 72

4-(1-Decanoyl)benzaldehyde

Tetrakis(triphenylphosphine)palladium(0) (50 mg) was added to a solution of 4-formylphenylboronic acid (0.50 g, 3.33 mmol), nonanoyl chloride (1.7 mL, 8.33 mmol) and cesium carbonate (2.70 g, 8.33 mmol) in toluene (40 mL) and heated to 80 °C. After stirring overnight, the reaction was diluted with ethyl acetate (50 mL) and washed with 2N hydrochloric acid (50 mL), sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 6% ethyl acetate/hexane gave 0.022 g (0.083 mmol, 3%) of product: ^{1}H NMR (500 MHz) δ 10.1 (s, 1H), 8.09 (d, J=8.2 Hz, 2H), 7.98 (d, J=8.2 Hz, 2H), 3.00 (t, J= 7.4 Hz, 2H), 1.70-1.80 (m, 2H), 1.22-1.42 (m, 12H), 0.88 (t, J=6.9 Hz, 3H).

Aldehyde 73

3-Methyl-4-decanoyl benzaldehyde

Step A: 4-Bromo-3-methylbenzyl alcohol

DIBALH (1.0M solution in methylene chloride, 31 mL, 31 mmol) was added dropwise to a solution of methyl 4-bromo-3-methylbenzoate (3.0 g, 14.0 mmol) in methylene chloride (20 mL) at 0 °C. After 1 h, the reaction was quenched with 10% aqueous sodium bisulfite (100 mL). The aqueous layer was separated and extracted with methylene chloride (50 mL). The combined organic layers were combined, dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 17% ethyl acetate/hexane gave 1.90 g (9.50 mmol, 68%)

of product: ^{1}H NMR (500 MHz) δ 7.50 (d, J=8.3 Hz, 1H), 7.24 (s, 1H), 7.04 (d, J=8.0 Hz, 1H), 4.62 (d, J= 5.7 Hz, 2H), 2.40 (s, 3H).

Step B: 4-(1-Hydroxydec-1-yl)-3-methylbenzyl alcohol

n-Butyllithium (2.5 M in hexanes, 8.3 mL, 20.7 mmol) was added dropwise to a solution of 4-bromo-3-methylbenzyl alcohol (1.90 g, 9.44 mmol, from Step A) in tetrahydrofuran (25 mL) at –78 °C. After 1 h, n-decanal (2.95 g, 18.89 mmol) was added and the reaction allowed to warm to 0°C. After 30 min, the reaction was quenched with water (25 mL) and diluted with ethyl acetate (25 mL). The organic layer was washed with sat'd sodium chloride (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 25% ethyl acetate/hexane gave 1.69 g (6.07 mmol, 64%) of product: ^{1}H NMR (500 MHz): δ 7.45 (d, J=8.0 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.14 (s, 1H), 4.88-4.94 (m, 1H), 4.64 (s, 2H), 2.34 (s, 3H), 1.22-1.80 (m, 16H), 0.87 (t, J=7.0 Hz, 3H).

Step C: 3-Methyl-4-decanoyl benzaldehyde

Dess-Martin periodinane (1.00 g, 2.37 mmol) was added to a solution of 4-(1-hydroxydec-1-yl)-3-methylbenzyl alcohol (0.300 g, 1.07 mmol, from Step B) in methylene chloride (5.0 mL). After 20 min, the reaction was filtered and concentrated *in vacuo*. Silica gel chromatography eluting with 5% ethyl acetate/hexane gave 0.24 g (0.89 mmol, 83%) of product: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.74 (s, 1H), 7.66 (d, J=7.8 Hz, 1H), 2.87 (t, J=7.5 Hz, 2H), 2.51 (s, 3H), 1.66-1.74 (m, 2H), 1.22-1.38 (m, 12H), 0.87 (t, J=7.0 Hz, 3H).

Aldehyde 74

3-Methyl-4-(4-(nonyl)benzoyl)benzaldehyde

The title compound was prepared using procedures analogous to those used to prepare Aldehyde 73 substituting 4-(nonyl)benzaldehyde for n-decanal in Step B: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.74 (s, 1H), 7.66 (d, J=7.8 Hz, 1H), 2.88 (t, J=7.5 Hz, 2H), 2.51 (s, 3H), 1.66-1.74 (m, 2H), 1.22-1.38 (m, 10H), 0.88 (t, J=7.0 Hz, 3H).

Aldehyde 75

3'-(1-Hydroxyhept-1-yl)-4-biphenylcarboxaldehyde

Step A: 1-Bromo-3-(1-hydroxyhept-1-yl)benzene

Hexylmagnesium bromide (2.0M in THF, 3.7 mL, 7.4 mmol) was added to a solution of 3-bromobenzaldehyde (1.50g, 8.11 mmol) in tetrahydrofuran (10 mL) at –78 °C. After 10 min, the reaction was quenched by the addition of 2N hydrochloric acid (30 mL) and the product extracted into ethyl acetate (30 mL). The organic layer was washed with sat'd sodium chloride (25 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 17% ethyl acetate/hexane gave 1.42 g (5.25 mmol, 65%) of product.

Step B: 3'-(1-Hydroxyhept-1-yl)-4-biphenylcarboxaldehyde

To a solution of 1-bromo-3-(1-hydroxyhept-1-yl)benzene (1.00 g, 3.70 mmol, from Step A), 4-formylphenylboronic acid (0.83 g, 5.55 mmol) and potassium fluoride (0.65 g, 11.10 mmol) in tetrahydrofuran (10 mL) was added palladium(II) acetate (0.016 g, 0.071 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.052 g, 0.148 mmol). After stirring for 24 h at rt, the reaction was diluted with ethyl acetate (50 mL), washed with water (50 mL), sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated in vacuo. Silica gel chromatography eluting with 25% ethyl acetate/hexanes gave 0.81 g of product as a yellow oil.

Aldehyde 76

3'-(Heptanoyl)-4-biphenylcarboxaldehyde

Step A: 1-Bromo-3-heptanoyl benzene

Dess-Martin periodinane (4.40 g, 15% solution in methylene chloride, 1.56 mmol) was added to a solution of 1-bromo-3-(1-hydroxyhept-1-yl)benzene (0.39 g, 1.42 mmol, from Aldehyde 75, Step A). After 1 h, the reaction was quenched by the addition of 1N sodium hydroxide (20 mL). The aqueous layer was separated, washed with methylene chloride (20 mL) and the organic layers combined, dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 5% ethyl acetate/hexane gave 0.30 g (1.11 mmol, 78%) of product: ^{1}H NMR (500 MHz) δ 8.08 (t, J=1.7 Hz, 1H), 7.87 (d, J=7.7 Hz, 1H), 7.68 (d, J=8.0 Hz, 1H), 7.34 (t,

J=7.9 Hz, 1H), 2.93 (t, J=7.4 Hz, 2H), 1.68-1.76 (m, 2H), 1.28-1.40 (m, 6H), 0.89 (t, J=7.0 Hz, 3H).

Step B: 3'-(Heptanoyl)-4-biphenylcarboxaldehyde

To a solution of 1-bromo-3-heptanoyl benzene (0.30 g, 1.11 mmol, from Step A), 4-formylphenylboronic acid (0.25 g, 1.68 mmol) and potassium fluoride (0.20 g, 3.36 mmol) in tetrahydrofuran (2.5 mL) was added palladium(II) acetate (0.006 g, 0.025 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.016 g, 0.050 mmol). After stirring for 3 h at 50°C, the reaction was placed onto silica gel and eluted with 10% ethyl acetate/hexanes to give 0.26 g (0.88 mmol, 80%) of product as a yellow oil: ^{1}H NMR (500 MHz) δ 8.22 (t, J=1.7 Hz, 1H), 7.90-8.10 (m, 3H), 8.30 (d, J=8.0 Hz, 1H), 7.99 (d, J=8.3 Hz, 2H), 7.58 (t, J=7.8 Hz, 1H), 3.02 (t, J=7.4 Hz, 2H), 1.66-1.80 (m, 2H), 1.38-1.44 (m, 2H), 1.30-1.38 (m, 4H), 0.90 (t, J=7.0 Hz, 3H).

Aldehyde 77

3-(Cyclopropyloxy)-4-(nonyloxy)benzaldehyde

To a solution of 1.78 g (10.0 mmol) of 3-(cyclopropyloxy)-4-hydroxybenzaldehyde and 2.54 g(10.0 mmol) of 1-iodononane in 20 mL acetonitrile was added 3.58 g(11.0 mmol) of Cs_2CO_3. The slurry was stirred at rt for 12 h. The reaction was quenched with 30 mL of water and extracted with ethyl acetate (50 mL x 2). The combined extractions were washed with water, dried with sodium sulfate and concentrated to a solid. Flash chromatography on a Biotage 40M cartridge using 10 % ethyl acetate/hexanes afforded 2.9 g (95%) of the title compound as a white solid. ^{1}H NMR (500 Mhz) δ 0.87-0.91 (m, 7H), 1.30-1.90 (m, 14H), 3.85 (m, 1H), 4.10 (t, J = 6.9, 2H), 6.98 (d, J = 8.2, 1H), 7.48 (dd, J = 8.5, 1.8, 1H), 7.77 (d, J = 1.8, 1H), 9.89 (s, 1H); LC-1: 4.6 min; ESI-MS 305 (M+H).

Aldehyde 78

4-(Nonylthio)benzaldehyde

To a solution of 3.15 g (10.0 mmol) of 1-bromo-4-(nonylthio)benzene in 50 mL anhydrous THF was slowly added 9.4 mL of *n*-BuLi (1.6 M in hexanes, 15 mmol) at –50 °C. The mixture was aged at the same temperature for 1 h before the addition of 2.3 mL of anhydrous DMF. The reaction mixture was allowed to warm to 0 °C and

was quenched with 2 N HCl to pH=1. The layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layer and extractions were washed with water and concentrated to oil. Flash chromatography on a Biotage 40M cartridge using 5 % ethyl acetate/hexanes afforded 2.35 g (89%) of the title compound as light yellow oil: ^{1}H NMR (500 MHz) δ 0.91 (t, J = 7.0, 3H), 1.30-1.76 (m, 14H), 3.03 (t, J = 7.4, 2H), 7.37 (d, J = 8.5, 2H), 7.78 (d, J = 8.5, 2H), 9.95 (s, 1H); LC-1: 4.8 min; ESI-MS 265 (M+H).

Aldehyde 79

3-(4-(Formyl)phenyl)-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

Step A: (E/Z)-2-Phenyl-3-chloro-4,4,4-trifluoro-2-butanal

Phosphorous oxychloride (7.5 mL, 80 mmol) was added to 15 mL of DMF at 0 °C. The resulting mixture was warmed to rt and stirred for 1 h. A solution of 5.0 g (26.6 mmol) of 1,1,1-trifluoromethyl-3-phenyl-2-propanone in 1 mL of DMF was added and the resulting mixture was stirred at 70 °C for 20 h. The reaction mixture was cooled to rt, poured onto 150 g of ice and stirred at ambient temperature for 1 h. The quenched mixture was extracted with 200 mL of ether. The extract was washed with 200 mL of water, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (4L) as the eluant afforded 5.1 g (82%) of the title compound.

Step B: Ethyl (4-phenyl-5-trifluoromethyl)thiophene-2-carboxylate

Ethyl mercaptoacetate (2.75 mL, 25.0 mmol) was added to a suspension of 600 mg (25 mmol) of NaH in 45 mL of THF maintaining the internal temperature at 25 °C. A solution of 5.10 g (21.7 mmol) of (E/Z)-2-phenyl-3-chloro-4,4,4-trifluoro-2-butanal (from Step A) was added and the resulting mixture was stirred at rt for 20 h. The reaction was quenched with 50 mL of sat'd NH_4Cl and the resulting mixture was partitioned between 250 mL of ether and 100 mL of water. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (1L), then 4:1 v/v hexanes/CH_2Cl_2 (1L) as the eluant afforded 5.10 g (78%) of the title compound: ^{1}H NMR (400 Mhz) δ 1.40 (t, J= 7.2, 3H), 4.39 (q, J= 7.2, 2H), 7.42 (app s, 5H), 7.74 (q, J=1.6, 1H).

Step C: (4-Phenyl-5-trifluoromethyl)thiophene-2-carboxylic acid

A solution of 5.10 g (17.0 mmol) of ethyl 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylate (from Step B) in 20 mL of EtOH was treated with 10 mL of 5.0 N NaOH and stirred at rt for 30 min. The EtOH was removed in vacuo. The residual aqueous mixture was acidified to pH 2 with 1 N HCl, then extracted with 300 mL of 1:1 v/v EtOAc/ether. The extract was separated, dried and concentrated. Recrystallization from 200 mL of 20:1 v/v hexanes/ether afforded 4.30 g (93%) of the title compound: ^{1}H NMR (500 Mhz) δ 7.43 (app s, 5H), 7.84 (app s, 1H); ^{13}C NMR ($CDCl_3$, 125 Mhz) δ 121.7 (q, J= 269), 128.5, 128.6, 128.8, 132.5 (q, J= 36), 133.3, 133.8, 137.5, 144.8, 167.0.

Step D: 3-[4-(Carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 408 mg (1.5 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid and 1 mL of oxalyl chloride in 5 mL of CH_2Cl_2 was treated with 5 drops of DMF. The resulting mixture was stirred at rt for 1 h, then concentrated. The crude acid chloride and 291 mg (1.5 mmol) of 4-(carbomethoxy)benzamidoxime were dissolved in 7 mL of 6:1 v/v xylenes/pyridine. The resulting solution was heated at 140 °C for 1 h, then cooled. The mixture was partitioned between 50 mL of 1:1 EtOAc/ether and 50 mL of 1 N HCl. The organic layer was separated, washed with 3 x 50 mL of 1 N HCl, 50 mL of sat'd $NaHCO_3$, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (1L), then 20:1 v/v hexanes/EtOAc (1L) as the eluant afforded 423 mg (65%) of the title compound: ^{1}H NMR (500 Mhz) δ 3.97 (s, 3H), 7.48 (app s, 5H), 7.92 (s, 1H), 8.18 (app d, J= 8.5, 2H), 8.23 (app d, J= 8.5, 2H).

Step E: 3-[4-(Hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 390 mg (0.91 mmol) of 3-[4-(carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step D) in 10 mL of CH_2Cl_2 at –78 °C was treated with 2.7 mL of 1.0 M DIBALH solution in CH_2Cl_2. The resulting solution was stirred cold for 1 h, then quenched with 5 mL of sat'd

Rochelle salt solution. The mixture was partitioned between 100 mL CH_2Cl_2 and 50 mL of 1 N NaOH. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 S cartridge using 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 325 mg (89%) of the title compound: ^{1}H NMR (500 Mhz) δ 1.80 (app s, 1H), 4.80 (d, J= 4.0, 2H), 7.46-7.48 (5H), 7.52 (d, J= 8.0, 2H), 7.91 (q, J= 1.5, 1H), 8.14 (d, J= 8.0, 2H).

Step F: 3-[4-(Formyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A mixture of 310 mg (0.77 mmol) of 3-[4-(hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step E), 527 mg (1.5 mmol) of 4-methylmorpholine N-oxide and 500 mg of 4 A molecular sieves in 15 mL of CH_3CN was treated with 12 mg (0.034 mmol) of tetrapropylammonium perruthnate and the resulting mixture was stirred ar rt for 2 h. The solids were filtered and the filtrated was concentrated. Chromatography on a Biotage 40 S cartridge using 9:1 v/v hexanes/EtOAc (1L) as the eluant afforded 205 mg (66%) of the title compound: ^{1}H NMR (500 Mhz) δ 7.48 (app s, 5H), 7.93 (app s, 1H), 8.03 (d, J= 8.5, 2H), 8.33 (d, J= 8.5, 2H), 10.1 (s, 1H).

Aldehyde 80

4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzaldehyde

Step A: 2-Hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene

A solution of 2.10 g (7.7 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid (from Aldehyde 17, Step C) in 20 mL of THF was treated with 5.0 mL of 2.0 M borane dimethylsulfide complex in THF. The resulting solution was heated at reflux for 3 h, cooled to rt, quenched with 10 mL of MeOH and concentrated. Chromatography on a Biotage 40M cartridge using 9:1 v/v hexanes/EtOAc as the eluant afforded 1.95 g (98%) of the title compound: ^{1}H NMR (500 Mhz) δ 2.05 (app s, 1H), 4.87 (s, 2H), 6.99 (s, 1H), 7.41 (app s, 5H).

Step B: 4-((4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

A solution of 1.95 g (7.5 mmol) of 2-hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene (from Step A), 925 mg (7.6 mmol) of 4-hydroxybenzaldehyde and 3.0 g (11.4 mmol) of triphenylphosphene in 40 mL of THF at 0 °C was treated with 2.0 g (11.4 mmol) of diethylazodicarboxylate. The resulting mixture was warmed to rt, stirred for 2 h, then concentrated. Chromatography on a Biotage 75S cartridge using 9:1 v/v heptane/EtOAc as the eluant afforded 2.5 g of impure title compound. Chromatography on a Biotage 40M cartridge using 19:1 v/v hexanes/EtOAc (1L), then 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 1.65 g (60%) of the title compound: ^{1}H NMR (500 Mhz) δ 5.32 (s, 2H), 7.10 (d, J= 8.5, 2H), 7.12 (s, 1H), 7.41-7.43 (5H), 7.85-7.90 (2H), 9.92 (s, 1H).

PREPARATION OF EXAMPLES

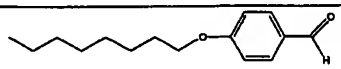
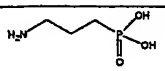
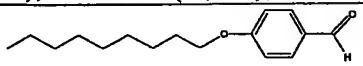
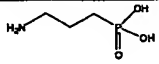
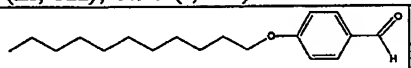
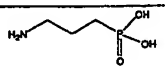
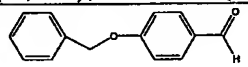
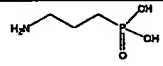
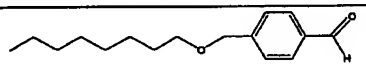
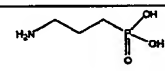
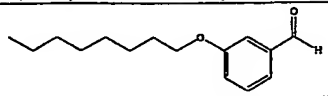
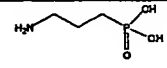
EXAMPLE 1

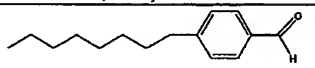
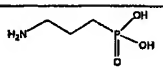
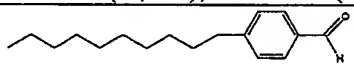
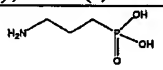
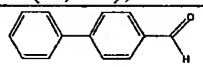
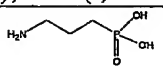
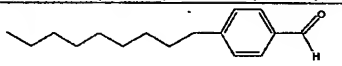
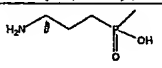
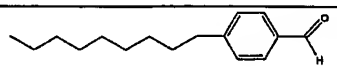
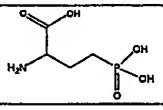
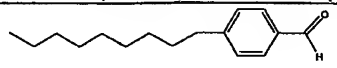
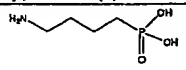
N-((4-Decyloxy)benzyl)-3-aminopropylphosphonic acid

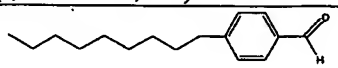
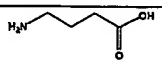
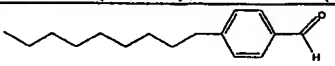
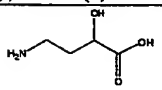
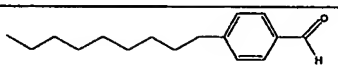
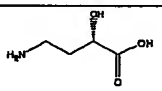
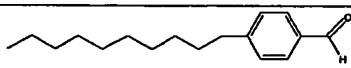
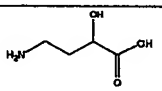
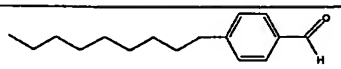
3-Aminopropylphosphonic acid (0.064 g, 0.457 mmol) and tetrabutylammonium hydroxide (1.0M in methanol, 0.46 mL, 0.46 mmol) in methanol (3 mL) were heated at 50 °C for 1 h to dissolve all solids. 4-(Decyloxy)benzaldehyde (0.100g, 0.381 mmol) and sodium cyanoborohydride (0.025 g, 0.40 mmol) were added and stirring was continued for 1 h at 50 °C. The reaction mixture was made acidic (pH~5) by the addition of concentrated HCl then directly purified by LC-3 to give the title compound (0.055 g): ^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.7 Hz, 2H), 6.98 (d, J=8.7 Hz, 2H), 4.12 (s, 2H), 3.99 (t, J=6.4 Hz, 2H), 3.12 (t, J=7.7 Hz, 2H), 2.0 (m, 2H), 1.64-1.84 (m, 4H), 1.47 (m, 2H), 1.24-1.40 (m, 12H), 0.90 (t, J=6.9 Hz, 3H); MS *m/e* 386.4 (M+H).

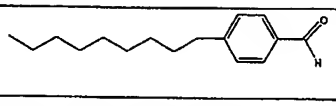
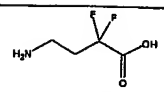
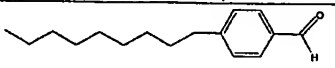
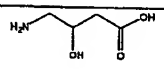
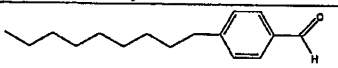
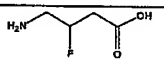
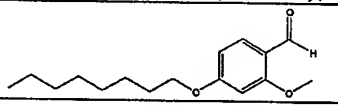
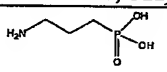
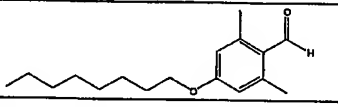
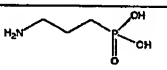
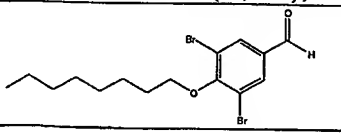
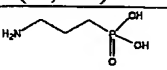
EXAMPLES 2-107

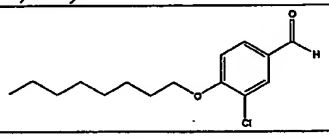
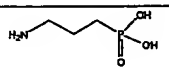
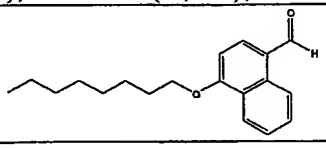
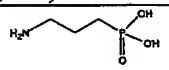
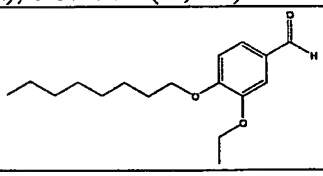
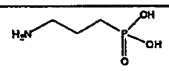
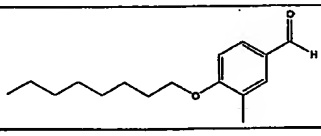
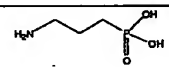
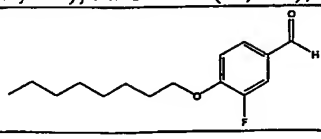
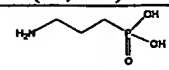
The following Examples (2-112) were prepared using a procedure analogous to that described in EXAMPLE 1 substituting A for 4-(decyloxy)benzaldehyde and B for 3-aminopropylphosphonic acid.

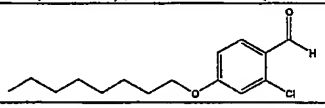
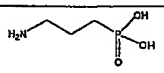
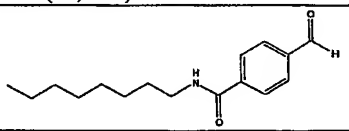
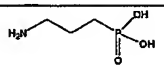
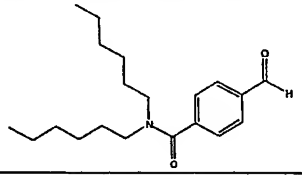
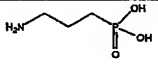
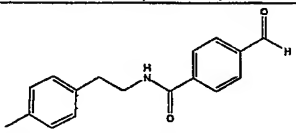
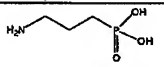
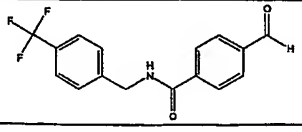
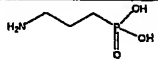
EXAMPLE	A	B	ESI-MS
2			358.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.35-7.41 (m, 2H), 6.94-7.01 (m, 2H), 4.08-4.13 (m, 2H), 3.96-4.02 (m, 2H), 3.08-3.14 (m, 2H), 1.93-2.04 (m, 2H), 1.73-1.82 (m, 4H), 1.43-1.51 (m, 2H), 1.26-1.41 (m, 8H), 0.87-0.94 (m, 3H).			
3			372.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, 2H), 6.98 (d, 2H), 4.86 (s, 19H), 4.12 (s, 2H), 3.98 (t, 2H), 3.12 (t, 2H), 1.94-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.42-1.52 (m, 2H), 1.24-1.41 (m, 8H), 0.90 (t, 3H).			
4			400.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.36-7.40 (m, 2H), 6.95-7.01 (m, 2H), 4.12 (s, 2H), 3.95-4.02 (m, 2H), 3.09-3.15 (m, 2H), 1.94-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.42-1.52 (m, 2H), 1.24-1.42 (m, 8H), 0.87-0.94 (m, 3H).			
5			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.33-7.44 (m, 5H), 7.27-7.33 (m, 2H), 7.03-7.09 (m, 2H), 5.11 (s, 2H), 4.11 (s, 2H), 3.07-3.15 (m, 2H), 1.92-2.04 (m, 2H), 1.73-1.82 (m, 2H).			
6			372.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.42-7.50 (m, 4H), 4.52 (s, 2H), 4.18 (s, 2H), 3.46-3.52 (m, 2H), 3.11-3.18 (m, 2H), 1.95-2.06 (m, 2H), 1.75-1.85 (m, 2H), 1.56-1.64 (m, 2H), 1.25-1.34 (m, 6H), 0.85-0.92 (m, 3H).			
7			358.2

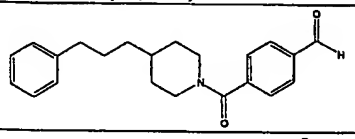
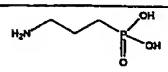
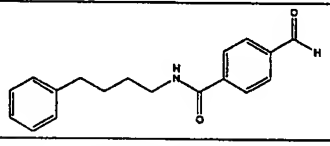
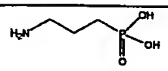
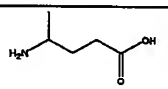
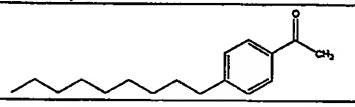
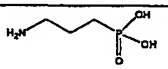
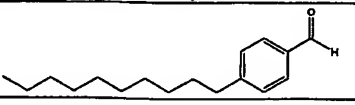
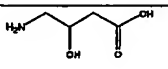
^{1}H NMR (500 MHz , CD_3OD) δ 7.34 (t, J=7.9 Hz, 1H), 7.05 (d, J=2.3 Hz, 1H), 7.03 (d, J=7.8 Hz, 1H), 6.98 (dd, J=2.3, 8.4 Hz), 4.12 (s, 2H), 4.00 (t, J=6.5 Hz, 2H), 3.12 (t, J=6.9 Hz, 2H), 1.94-2.20 (m, 2H), 1.70-1.82 (m, 4H), 1.44-1.52 (m, 2H), 1.26-1.40 (m, 8H), 0.90 (t, J=6.9 Hz, 3H).			
8			342.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.14 (t, J=7.7 Hz, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.00 (m, 2H), 1.81 (td, J= 7.6, 18.5 Hz, 2H), 1.58-1.64 (m, 2H), 1.22-1.36 (m, 10H), 0.89 (t, J=7.0 Hz, 3H).			
9			370.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.14 (t, J=7.7 Hz, 2H), 2.64 (t, J= 7.6 Hz, 2H), 2.00 (m, 2H), 1.80 (td, J= 7.6, 18.5 Hz, 2H), 1.56-1.64 (m, 2H), 1.24-1.38 (m, 14H), 0.89 (t, J=7.0 Hz, 3H).			
11			306.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (m, 2H), 7.63 (m, 2H), 7.56 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 4.24 (s, 2H), 3.18 (t, 2H), 1.97-2.08 (m, 2H), 1.76-1.86 (m, 2H).			
12			354.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.12 (t, J=7.3 Hz, 2H), 2.64 (t, J= 7.6 Hz, 2H), 1.98 (m, 2H), 1.76-1.84 (m, 2H), 1.58-1.64 (m, 2H), 1.43 (d, J=14 Hz, 3H), 1.24-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
13			400.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.41 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.14-4.22 (m, 2H), 4.04 (t, J=6.0 Hz, 1H), 2.64 (t, J= 7.6 Hz, 2H), 2.20-2.30 (m, 2H), 1.74-1.98 (m, 2H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 12H), 0.90 (t, J=7.0 Hz, 3H).			
14			370.3

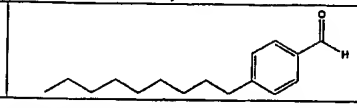
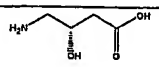
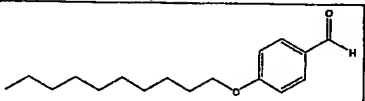
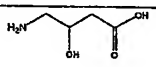
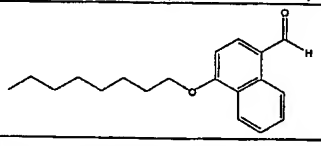
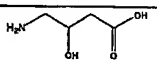
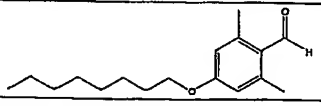
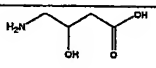
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.1 Hz, 2H), 4.15 (s, 2H), 3.05 (t, J=7.8 Hz, 2H), 2.64 (t, J= 7.7 Hz, 2H), 1.58-1.984 (m, 8H), 1.24-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
15			320.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.10 (t, J=7.8 Hz, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.45 (t, J= 7.0 Hz, 2H), 1.93-1.99 (m, 2H), 1.56-1.64 (m, 2H), 1.24-1.34 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
16			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.1 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 4.26 (dd, J=4.1, 7.8 Hz, 1H), 4.17 (s, 2H), 3.16-3.22 (m, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.16-2.24 (m, 1H), 1.98-2.06 (m, 1H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
17			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.26 (dd, J=4.1, 8.0 Hz, 1H), 4.17 (s, 2H), 3.16-3.22 (m, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.16-2.24 (m, 1H), 1.98-2.06 (m, 1H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			
18			350.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.26 (dd, J=4.3, 8.0 Hz, 1H), 4.17 (s, 2H), 3.16-3.22 (m, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.16-2.24 (m, 1H), 1.98-2.06 (m, 1H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 14H), 0.89 (t, J=7.0 Hz, 3H)			
19			344.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=7.0 Hz, 2H), 7.28 (d, J=7.8 Hz, 2H), 4.18 (s, 2H), 3.17 (t, J=7.4 Hz, 2H), 3.06 (t, J=7.4 Hz, 2H), 2.64 (t, J= 7.6 Hz, 2H), 2.20 (m, 2H), 1.56-1.64 (m, 2H), 1.22-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			

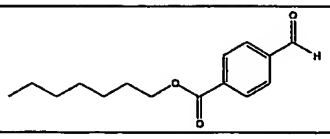
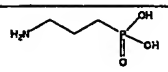
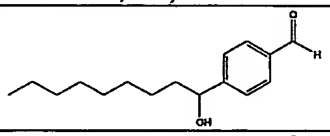
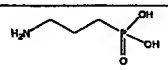
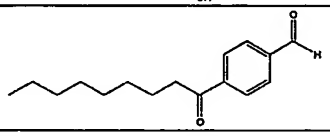
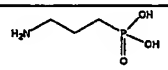
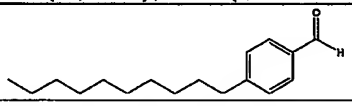
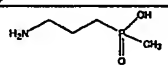
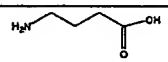
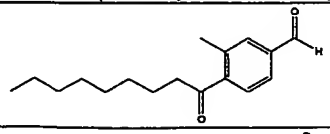
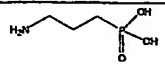
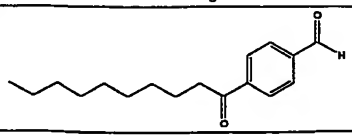
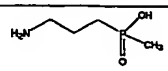
20			356.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.2 Hz, 2H), 7.03 (d, J=7.8 Hz, 1H), 4.20 (s, 2H), 2.65 (t, J=7.7 Hz, 2H), 2.49-2.60 (m, 2H), 1.58-1.64 (m, 2H), 1.24-1.34 (m, 14H), 0.89 (t, J=7.0 Hz, 3H)			
21			336.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 4.25-4.31 (m, 1H), 4.19 (s, 2H), 3.18 dd, J=2.9, 12.5 Hz, 1H), 2.98 (dd, J= 9.9, 12.6 Hz, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.53 (d, J=6.2 Hz, 2H), 1.56-1.64 (m, 2H), 1.24-1.34 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			
22			338.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.40 (d, J=8.0 Hz, 2H), 7.30 (d, J=7.7 Hz, 2H), 5.14-5.32 (m, 1H), 4.23 (m, 2H), 3.34-3.42 (m, 2H), 2.74-2.82 (m, 2H), 2.65 (t, J= 7.7Hz, 2H), 1.56-1.63 (m, 2H), 1.24-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			
23			388.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.24-7.28 (m, 1H), 6.60-6.63 (m, 1H), 6.53-6.57 (m, 1H), 4.11 (s, 2H), 3.96-4.02 (m, 2H), 3.88-3.92 (m, 3H), 3.28-3.33 (m, 2H), 3.06-3.12 (m, 2H), 1.94-2.05 (m, 2H), 1.72-1.82 (m, 4H), 1.43-1.52 (m, 2H), 1.26-1.41 (m, 8H), 0.87-0.94 (m, 3H)			
24			386.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.68 (s, 2H), 4.20-4.25 (m, 2H), 3.91-3.97 (m, 2H), 3.22-3.27 (m, 2H), 2.41 (s, 6H), 1.99-2.10 (m, 2H), 1.78-1.87 (m, 2H), 1.69-1.78 (m, 2H), 1.41-1.50 (m, 2H), 1.26-1.40 (m, 8H), 0.86-0.94 (m, 3H)			
25			516.1

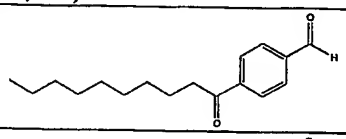
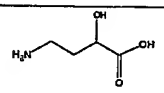
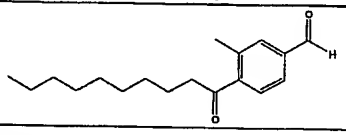
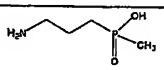
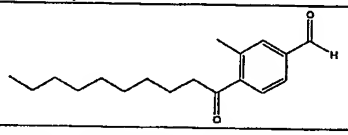
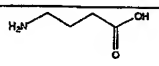
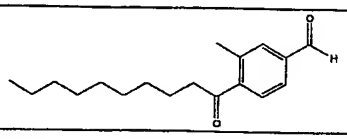
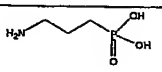
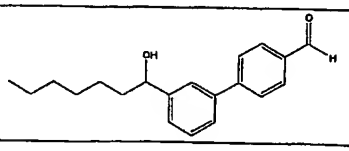
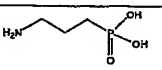
^{1}H NMR (500 MHz , CD_3OD) δ 7.78 (s, 2H), 4.14 (s, 2H), 4.00-4.05 (m, 2H), 3.12-3.18 (m, 2H), 1.94-2.04 (m, 2H), 1.76-1.90 (m, 4H), 1.52-1.59 (m, 2H), 1.29-1.44 (m, 8H), 0.88-0.94 (m, 3H)			
26			392.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.52-7.54 (m, 1H), 7.34-7.38 (m, 1H), 7.08-7.13 (m, 1H), 4.04-4.14 (m, 4H), 3.09-3.16 (m, 2H), 1.93-2.04 (m, 2H), 1.73-1.85 (m, 4H), 1.46-1.55 (m, 2H), 1.26-1.42 (m, 8H), 0.87-0.94 (m, 3H)			
27			408.3
^{1}H NMR (500 MHz , CD_3OD) δ 8.35-8.38 (m, 1H), 8.05-8.09 (m, 1H), 7.64-7.70 (m, 1H), 7.54-7.62 (m, 2H), 6.94-6.98 (m, 1H), 4.61 (s, 2H), 4.18-4.24 (m, 2H), 3.21-3.27 (m, 2H), 1.99-2.08 (m, 2H), 1.91-1.99 (m, 2H), 1.75-1.85 (m, 2H), 1.55-1.64 (m, 2H), 1.27-1.48 (m, 8H), 0.87-0.94 (m, 3H)			
28			402.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.05-7.08 (m, 1H), 6.98-7.01 (m, 2H), 4.06-4.14 (m, 3H), 3.98-4.04 (m, 2H), 3.28-3.32 (m, 2H), 3.08-3.15 (m, 2H), 1.94-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.45-1.52 (m, 2H), 1.38-1.44 (m, 2H), 1.26-1.38 (m, 8H), 0.86-0.94 (m, 3H)			
29			372.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.22-7.27 (m, 2H), 6.91-6.95 (m, 1H), 4.07 (s, 2H), 3.97-4.03 (m, 2H), 3.07-3.14 (m, 2H), 2.22 (s, 3H), 1.93-2.04 (m, 2H), 1.73-1.84 (m, 4H), 1.46-1.54 (m, 2H), 1.26-1.42 (m, 8H), 0.86-0.93 (m, 3H)			
30			

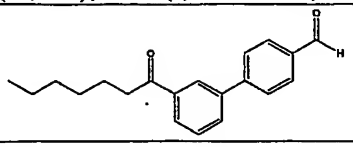
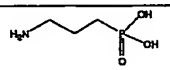
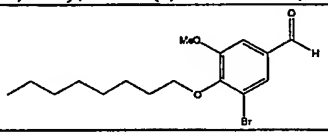
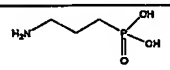
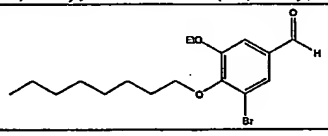
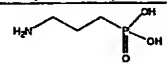
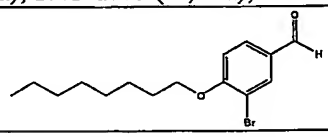
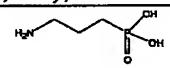
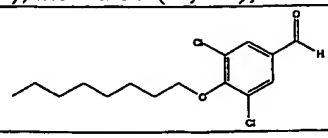
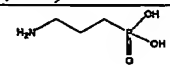
^{1}H NMR (500 MHz , CD_3OD) δ 7.19-7.28 (m, 2H), 7.11-7.16 (m, 1H), 4.11 (s, 2H), 4.03-4.08 (m, 2H), 3.09-3.15 (m, 2H), 1.93-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.44-1.54 (m, 2H), 1.26-1.42 (m, 8H), 0.86-0.94 (m, 3H)			
31			392.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.48 (d, J=8.5 Hz, 1H), 7.09 (d, J=2.3 Hz, 1H), 6.96 (dd, J=2.6, 8.6, 1H), 4.28 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.29-3.30 (m, 2H), 3.18 (t, J=7.4 Hz, 2H0, 1.97-2.08 (m, 2H), 1.73-1.84 (m, 4H0, 1.42-1.52 (m, 2H), 1.26-1.41 (m, 8H), 0.87-0.94 (m, 3H)			
32			385.4
^{1}H NMR (500 MHz , CD_3OD) δ 7.86-7.91 (m, 2H), 7.56-7.60 (m, 2H), 4.24 (s, 2H), 3.34-3.40 (m, 2H), 3.14-3.19 (m, 2H), 1.95-2.07 (m, 2H), 1.74-1.84 (m, 2H), 1.58-1.67 (m, 2H), 1.25-1.43 (m, 10H), 0.86-0.92 (m, 3H)			
33			441.5
^{1}H NMR (500 MHz , CD_3OD) δ 7.56-7.60 (m, 2H), 7.42-7.46 (m, 2H), 4.23 (s, 2H), 3.46-3.52 (m, 2H), 3.20-3.26 (m, 2H), 3.14-3.20 (m, 2H), 1.94-2.06 (m, 2H), 1.73-1.84 (m, 2H), 1.64-1.72 (m, 2H), 1.45-1.56 (m, 2H), 1.32-1.44 (m, 8H), 1.18-1.27 (m, 2H), 1.04-1.18 (m, 2H), 0.88-0.98 (m, 3H), 0.80-0.88 (m, 3H)			
34			391.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.85 (d, J=8.3 Hz, 2H), 7.57 (d, J=8.2 Hz, 2H), 7.12 (d, J=8.1Hz, 2H), 7.09 (d, J=8.0 Hz, 2H), 4.25 (s, 2H), 3.58 (t, J=7.4 Hz, 2H), 3.17 (t, J=7.6 Hz, 2H), 2.87 (t, J=7.5, 2H), 2.28 (s, 3H), 1.98-2.03 (m, 2H), 1.79-1.84 (m, 2H)			
35			431.1

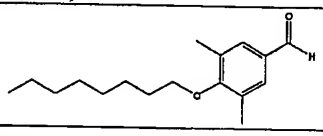
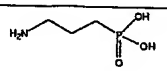
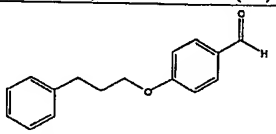
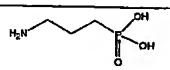
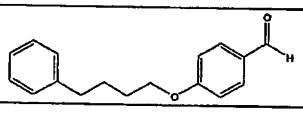
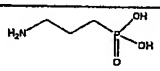
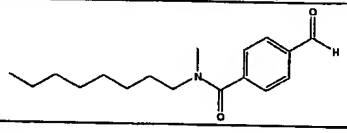
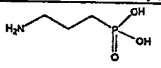
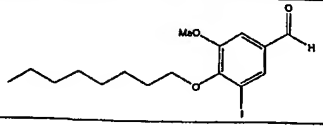
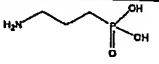
^{1}H NMR (500 MHz , CD_3OD) δ 7.95 (d, J=8.3 Hz, 2H), 7.63 (d, J=8.0, 2H), 7.60 (d, J=8.2, 2H), 7.54 (d, J=8.0 Hz, 2H), 4.65 (s, 2H), 4.26 (s, 2H). 3.17 (t, J=7.3, 2H), 1.98-2.06 (m, 2H), 1.75-1.84 (m, 2H)			
36			459.2
37			405.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.88 (d, J=8.2 Hz, 2H), 7.57 (d, J=8.2 Hz, 2H), 7.23 (t, J=7.5, 2H), 7.18 (d, J=7.1, 2H), 7.13 (t, J=7.2 Hz, 1H), 4.24 (s, 2H), 3.37-3.43 (m, 2H), 3.13-3.20 (m, 2H), 2.62-2.70 (m, 2H), 1.95-2.06 (m, 2H), 1.74-1.84 (m, 2H), 1.60-1.74 (m, 4H)			
38			334.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.2 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.21 (d, J=13.0 Hz, 1H), 4.18 (d, J=13.0 Hz, 1H), 3.32-3.40 (m, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.52 (ddd, J=16.9, 7.5, 6.2 Hz, 1H), 2.43 (dt, J=17.2, 7.7 Hz, 1H), 2.12-2.20 (m, 1H), 1.76-1.86 (m, 1H), 1.56-1.65 (m, 2H), 1.38 (d, J=6.7 Hz, 3H), 1.22-1.34 (m, 12H), 0.90 (t, J= 6.3 Hz, 3H).			
39			370.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.37 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 4.33 (q, J=6.8 Hz, 1H), 3.00-3.08 (m, 1H), 2.82-2.88 (m, 1H), 2.64 (t, J=7.7 Hz, 2H), 1.90-2.00 (m, 2H), 1.70-1.80 (m, 2H), 1.65 (d, J= 6.9 Hz, 3H), 1.58-1.64 (m, 2H), 1.22-1.36 (m, 12H), 0.89 (t, J= 6.9 Hz, 3H).			
40			350.1

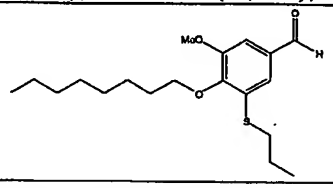
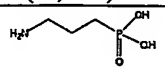
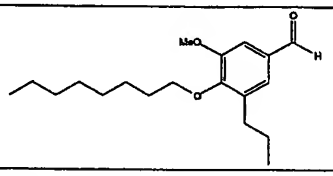
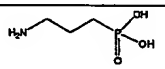
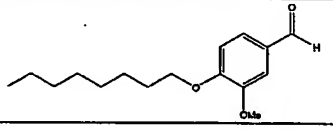
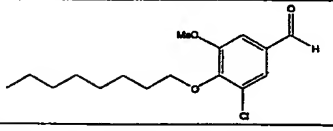
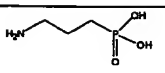
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.24-4.30 (m, 1H), 4.19 (s, 2H), 3.17 (dd, J=12.6, 3.0 Hz, 1H), 2.98 (dd, J=12.9, 9.9 Hz, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.52 (d, J=6.1 Hz, 2H), 1.58-1.65 (m, 2H), 1.24-1.35 (m, 14H), 0.89 (t, J= 7.0 Hz, 3H).			
41			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.24-4.30 (m, 1H), 4.19 (s, 2H), 3.17 (dd, J=12.6, 3.1 Hz, 1H), 2.98 (dd, J=12.9, 9.8 Hz, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.52 (d, J=6.1 Hz, 2H), 1.58-1.65 (m, 2H), 1.24-1.35 (m, 12H), 0.89 (t, J= 6.9 Hz, 3H).			
42			366.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.7 Hz, 2H), 6.98 (d, J=8.7 Hz, 2H), 4.25-4.30 (m, 1H), 4.16 (s, 2H), 3.99 (t, J=6.5 Hz, 2H), 3.16 (dd, J=12.5, 2.9 Hz, 1H), 2.96 (dd, J=12.8, 9.8 Hz, 1H), 2.52 (d, J=6.2 Hz, 2H), 1.74-1.80 (m, 2H), 1.44-1.51 (m, 2H), 1.22-1.40 (m, 12H), 0.90 (t, J= 7.0 Hz, 3H).			
43			388.1
^{1}H NMR (500 MHz , CD_3OD) δ 8.35 (d, J=8.5 Hz, 1H), 8.09 (d, J=8.5 Hz, 1H), 7.67 (t, J=8.4 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.57 (t, J=8.0 Hz, 1H), 6.96 (d, J=8.0 Hz, 1H), 4.66 (s, 2H), 4.32-4.38 (m, 1H) 4.21 (t, J=6.4 Hz, 2H), 3.26-3.32 (m, 1H), 3.08 (dd, J=12.8, 9.8 Hz, 1H), 2.55 (d, J=6.2 Hz, 2H), 1.91-1.98 (m, 2H), 1.56-1.62 (m, 2H), 1.28-1.48 (m, 8H), 0.90 (t, J= 6.9 Hz, 3H).			
44			366.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.69 (s, 2H), 4.35-4.40 (m, 1H), 4.33 (d, J=13.8 Hz, 1H), 4.26 (d, J=13.7 Hz, 1H), 3.95 (t, J=6.5 Hz, 2H), 3.30-3.35 (m, 1H), 3.09 (dd, J=12.8, 9.9 Hz, 1H), 2.56 (d, J=6.2 Hz, 2H), 2.42 (s, 6H), 1.71-1.78 (m, 2H), 1.42-1.48 (m, 2H), 1.28-1.38 (m, 8H), 0.90 (t, J= 7.0 Hz, 3H).			

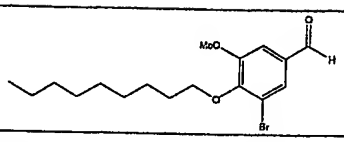
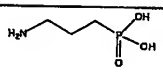
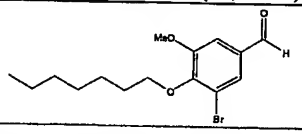
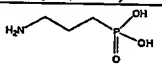
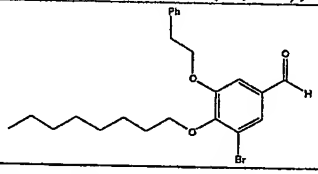
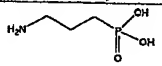
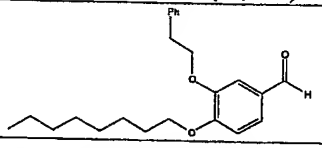
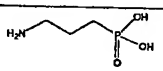
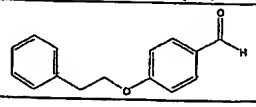
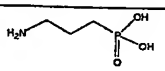
45			372.2
^{1}H NMR (500 MHz , CD_3OD) δ 8.12 (d, J=8.3 Hz, 2H), 7.65 (d, J=8.2 Hz, 2H), 4.36 (t, J=6.6 Hz, 2H), 4.30 (s, 2H), 3.21 (t, J=7.5 Hz, 2H), 2.00-2.10 (m, 4H), 1.32-1.52 (m, 8H), 0.93 (t, J= 7.0 Hz, 3H).			
46			372.2
47			370.2
^{1}H NMR (500 MHz , CD_3OD) δ 8.06 (d, J=8.3 Hz, 2H), 7.65 (d, J=8.3 Hz, 2H), 4.23 (s, 2H), 3.16 (t, J=6.1 Hz, 2H), 3.04 (t, J=7.4 Hz, 2H), 1.96-2.06 (m, 2H), 1.66-1.78 (m, 4H), 1.26-1.44 (m, 10H), 0.91 (t, J= 7.1 Hz, 3H).			
48			368.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.41 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 4.18 (s, 2H), 3.16 (t, J=7.4 Hz, 2H), 2.67 (t, J=7.7 Hz, 2H), 1.96-2.06 (m, 2H), 1.82-1.88 (m, 2H), 1.60-1.68 (m, 2H), 1.59 (d, J=14.2 Hz, 3H), 1.26-1.36 (m, 14H), 0.92 (t, J= 7.0 Hz, 3H).			
49			334.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.40 (d, J=8.1 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 4.18 (s, 2H), 3.12 (t, J=7.2 Hz, 2H), 2.67 (t, J=7.7 Hz, 2H), 2.48 (t, J=7.0 Hz, 2H), 1.94-2.02 (m, 2H), 1.60-1.68 (m, 2H), 1.26-1.38 (m, 14H), 0.92 (t, J= 7.0 Hz, 3H).			
50			384.2
51			382.2

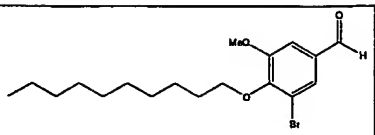
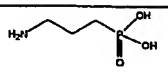
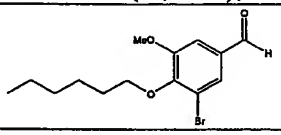
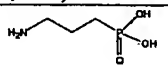
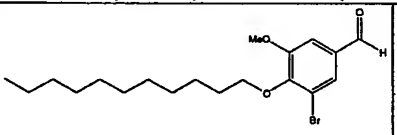
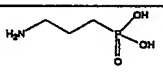
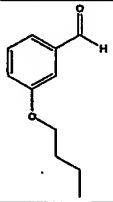
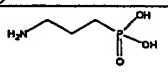
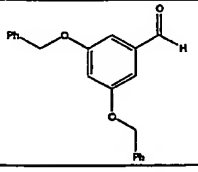
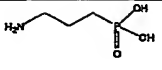
^{1}H NMR (500 MHz , CD_3OD) δ 8.30 (d, J=8.3 Hz, 2H), 7.65 (d, J=8.2 Hz, 2H), 4.25 (s, 2H), 4.30 (s, 2H), 3.20 (t, J=7.3 Hz, 2H), 3.01 (t, J=7.2 Hz, 2H), 2.00-2.08 (m, 2H), 1.82-1.90 (m, 2H), 1.68-1.76 (m, 2H), 1.48 (d, J=14.2 Hz, 3H), 1.26-1.44 (m, 12H), 0.92 (t, J= 7.1 Hz, 3H).			
52			364.1
53			396.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.77 (d, J=7.8 Hz, 1H), 7.42-7.43 (m, 2H), 4.22 (s, 2H), 3.17 (t, J=7.3 Hz, 2H), 2.93 (t, J=7.3 Hz, 2H), 2.48 (s, 3H), 1.96-2.06 (m, 2H), 1.82-1.88 (m, 2H), 1.64-1.70 (m, 2H), 1.47 (d, J=14.0 Hz, 3H), 1.28-1.38 (m, 12H), 0.90 (t, J= 7.0 Hz, 3H).			
54			362.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.76 (d, J=8.4 Hz, 1H), 7.41-7.43 (m, 2H), 4.23 (s, 2H), 3.14 (t, J=7.8 Hz, 2H), 2.93 (t, J=7.3 Hz, 2H), 2.48 (t, J=7.0 Hz, 2H), 2.47 (s, 3H), 1.96-2.04 (m, 2H), 1.64-1.70 (m, 2H), 1.26-1.40 (m, 12H), 0.91 (t, J= 7.0 Hz, 3H).			
55			398.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.76 (d, J=7.8 Hz, 1H), 7.42-7.43 (m, 2H), 4.21 (s, 2H), 3.18 (t, J=7.2 Hz, 2H), 2.93 (t, J=7.3 Hz, 2H), 2.48 (s, 3H), 1.98-2.08 (m, 2H), 1.80 (dt, J=18.1, 7.4 Hz, 2H), 1.64-1.71 (m, 2H), 1.26-1.40 (m, 12H), 0.91 (t, J= 7.0 Hz, 3H).			
56			420.3

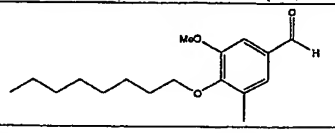
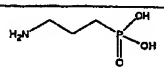
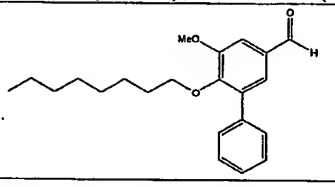
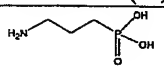
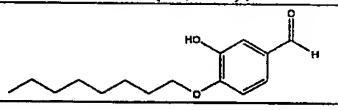
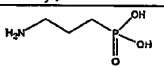
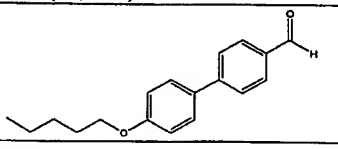
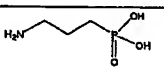
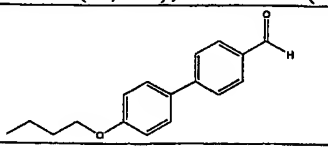
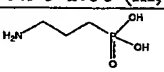
^{1}H NMR (500 MHz , CD_3OD) δ 7.76 (d, J=8.3 Hz, 2H), 7.64 (s, 1H), 7.59 (d, J=8.3 Hz, 2H), 7.55 (d, J=7.7 Hz, 1H), 7.45 (t, J=7.7 Hz, 1H), 7.37 (d, J=7.6 Hz, 1H), 4.70 (t, 6.8 Hz, 1H), 4.27 (s, 2H), 3.21 (t, J=7.6 Hz, 2H), 2.00-2.10 (m, 2H), 1.70-1.88 (m, 4H), 1.26-1.50 (m, 8H), 0.90 (t, J= 7.0 Hz, 3H).			
57			418.3
^{1}H NMR (500 MHz , CD_3OD) δ 8.23 (s, 1H), 8.04 (d, J=7.7 Hz, 1H), 7.91 (d, J=7.8 Hz, 1H), 7.80 (d, J=8.2 Hz, 2H), 7.62-7.66 (m, 3H), 4.28 (s, 2H), 3.22 (t, 7.5 Hz, 2H), 3.11 (t, J=7.2 Hz, 2H), 2.02-2.12 (m, 2H), 1.84 (dt, J=18.3, 7.4 Hz, 2H), 1.72-1.78 (m, 2H), 1.28-1.48 (m, 6H), 0.94 (t, J= 7.0 Hz, 3H).			
58			468.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.29 (s, 1H), 7.16 (s, 1H), 4.01 (s, 2H), 3.98 (t, J=6.4 Hz, 2H), 3.90 (s, 3H), 3.13 (t, J=6.7 Hz, 2H), 1.98-2.01 (m, 2H), 1.73-1.77 (m, 4H), 1.49-1.51 (m, 2H), 1.32-1.34 (m, 8H), 0.89-0.91 (m, 3H)			
59			357.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.28 (s, 1H), 7.13 (s, 1H), 4.12-4.13 (m, 2H), 4.09 (s, 3H), 4.00 (t, J=6.3, 2H), 3.12 (t, J=6.7, 2H), 1.96-2.04 (m, 2H), 1.73-1.78 (m, 4H), 1.48-1.56 (m, 2H), 1.43-1.46 (m, 2H), 1.32-1.37 (m, 8H), 0.88-0.93 (m, 3H)			
60			436.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.7 (s, 1H), 7.41 (d, J=8.5 Hz, 1H), 7.07 (d, J=8.4 Hz, 1H), 4.06-4.10 (m, 4H), 3.12 (t, J=7.2, 2H), 1.95-2.00 (m, 2H), 1.75-1.83 (m, 4H), 1.51-1.54 (m, 2H), 1.32-1.37 (m, 8H), 0.89-0.91 (m, 3H)			
61			426.1

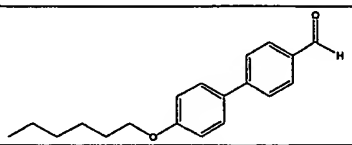
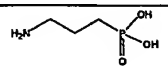
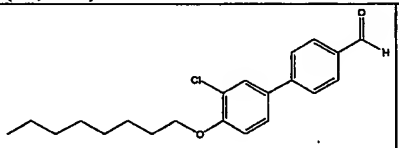
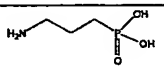
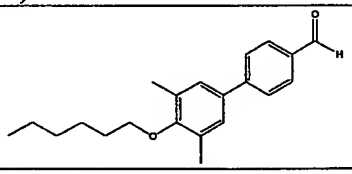
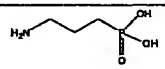
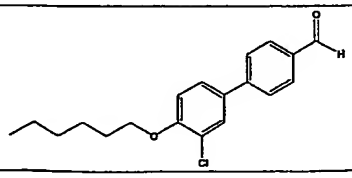
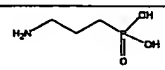
^{1}H NMR (500 MHz , CD_3OD) δ 7.56 (s, 1H), 4.13 (s, 2H), 4.02-4.04 (m, 2H), 3.13-3.12 (m, 2H), 1.98-2.00 (m, 2H), 1.75-1.84 (m, 4H), 1.49-1.58 (m, 2H), 1.26-1.42 (m, 8H), 0.89-0.91 (m, 3H)			
62			386.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.14 (s, 2H), 4.08 (s, 2H), 3.79 (t, J=6.4 Hz, 2H), 3.13 (t, J=7.6 Hz, 2H), 2.30 (s, 6H), 1.95-2.05 (m, 2H), 1.76-1.84 (m, 4H), 1.51-1.58 (m, 2H), 1.31-1.44 (m, 8H), 0.90-0.95 (m, 3H)			
63			364.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.40 (d, J=8.7 Hz, 2H), 7.26 (t, J=7.26 Hz, 2H), 7.17-7.22 (m, 3H), 6.99 (d, J=8.7 Hz, 2H), 4.13 (s, 2H), 3.99 (t, J=6.2 Hz, 2H), 3.13 (t, J=7.6 Hz, 2H), 2.81 (t, J=7.6 Hz, 2H), 2.06-2.12 (m, 2H), 1.95-2.04 (m, 2H), 1.76-1.85 (m, 2H)			
64			255.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.7 Hz, 2H), 7.26 (t, J=7.5 Hz, 2H), 7.20 (d, J=7.1 Hz, 2H), 7.14-7.18 (m, 1H), 6.98 (d, J=8.7 Hz, 2H), 4.12 (s, 2H), 4.02 (s, 2H), 3.12 (t, J=7.4 Hz, 2H), 2.66-2.72 (m, 2H), 1.94-2.04 (m, 2H), 1.76-1.84 (m, 6H)			
65			399.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.60 (d, J=7.8 Hz, 2H), 7.49 (t, J=7.3 Hz, 2H), 4.26 (s, 2H), 3.19 (t, J=7.4 Hz, 3H), 3.09 (s, 2H), 2.96 (s, 2H), 1.98-2.08 (m, 2H), 1.78-1.86 (m, 2H), 1.22-1.32 (m, 4H), 1.00-1.04 (m, 8H)), 0.88-0.94 (m, 3H)			
66			514.0

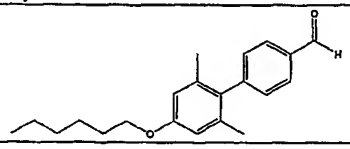
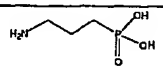
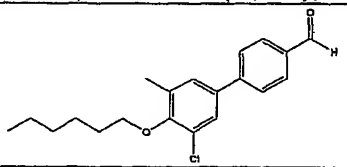
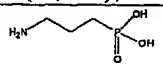
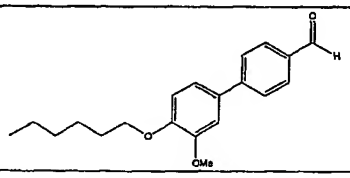
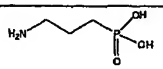
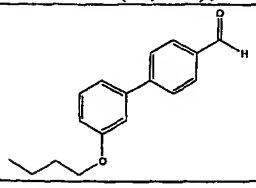
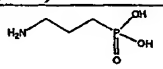
^{1}H NMR (500 MHz , CD_3OD) δ 7.51 (s, 2H), 7.18 (d, 2H), 4.12 (s, 2H), 3.99 (t, J=6.5 Hz, 2H), 3.90 (s, 3H), 3.15 (t, J=7.4 Hz, 2H), 1.96-2.06 (m, 2H), 1.75-1.84 (m, 4H), 1.50-1.56 (m, 2H), 1.29-1.41 (m, 8H), 0.89-0.95 (m, 3H)			
67			462.1
^{1}H NMR (500 MHz , CD_3OD) δ 6.99 (d, 2H), 4.14 (s, 2H), 3.97 (t, J=6.5 Hz, 2H), 3.89 (s, 3H), 3.15 (t, J=7.2 Hz, 2H), 2.93 (t, J=7.2 Hz, 2H), 1.96-2.06 (m, 2H), 1.66-1.84 (m, 6H), 1.48-1.56 (m, 2H), 1.28-1.42 (m, 8H), 1.04-1.10 (m, 3H), 0.90-0.96 (m, 3H)			
68			430.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.99 (s, 1H), 6.91 (s, 1H), 4.12 (s, 2H), 3.95 (t, J=6.4 Hz, 2H), 3.88 (s, 3H), 3.15 (t, J=7.4 Hz, 2H), 2.62 (t, J=7.8 Hz, 2H), 1.96-2.06 (m, 2H), 1.72-1.85 (m, 4H), 1.58-1.68 (m, 2H), 1.48-1.54 (m, 2H), 1.30-1.42 (m, 8H), 0.95-1.00 (m, 3H), 0.90-0.95 (m, 3H)			
69			386.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.10 (s, 1H), 7.00 (s, 2H), 4.12 (s, 2H), 4.02 (s, 2H), 3.89 (s, 3H), 3.10-3.16 (m, 2H), 1.94-2.04 (m, 2H), 1.73-1.83 (m, 4H), 1.62-1.71 (m, 2H), 1.26-1.52 (m, 8H), 0.88-0.96 (m, 3H)			
70			422.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.16 (s, 1H), 7.13 (s, 1H), 4.13 (s, 2H), 4.01 (t, J=6.6 Hz, 2H), 3.92 (s, 3H), 3.15 (t, J=7.2 Hz, 2H), 1.96-2.06 (m, 2H), 1.72-1.84 (m, 4H), 1.48-1.55 (m, 2H), 1.28-1.41 (m, 8H), 0.89-0.95 (m, 3H)			

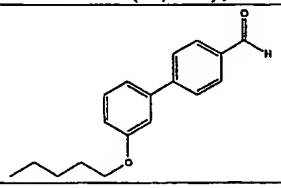
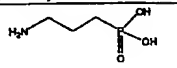
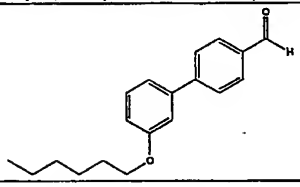
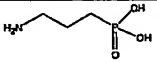
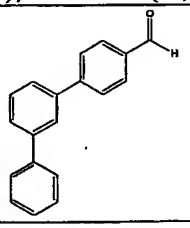
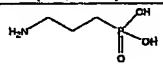
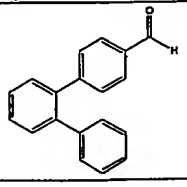
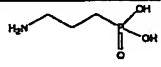
71			482.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.32 (d, 1H), 7.17 (d, 1H), 4.15 (s, 2H), 4.01 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.17 (t, J=7.6 Hz, 2H), 1.98-2.08 (m, 2H), 1.74-1.87 (m, 4H), 1.49-1.59 (m, 2H), 1.28-1.44 (m, 10H), 0.90-0.96 (m, 3H)			
72			454.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.32 (d, 1H), 7.17 (d, 1H), 4.15 (s, 2H), 4.01 (t, J=6.5 Hz, 2H), 3.92 (s, 3H), 3.17 (t, J=7.5 Hz, 2H), 1.98-2.08 (m, 2H), 1.75-1.86 (m, 4H), 1.49-1.56 (m, 2H), 1.32-1.43 (m, 6H), 0.92-0.96 (m, 3H)			
73			544.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.49 (d, J=7.3 Hz, 2H), 7.41 (t, J=7.4 Hz, 2H), 7.37 (d, J=7.3 Hz, 1H), 7.33 (s, 1H), 7.25 (s, 1H), 5.18 (s, 2H), 4.13 (s, 2H), 4.02 (t, J=6.4 Hz, 2H), 3.12 (t, J=7.3 Hz, 2H), 1.96-2.06 (m, 2H), 1.70-1.84 (m, 4H), 1.40-1.48 (m, 2H), 1.22-1.36 (m, 8H), 0.88-0.94 (m, 3H)			
74			464.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.47 (d, J=7.5 Hz, 2H), 7.38 (t, J=7.4 Hz, 2H), 7.33 (d, J=7.4 Hz, 1H), 7.15 (s, 1H), 7.04 (s, 2H), 5.16 (s, 2H), 4.09 (s, 2H), 4.05 (t, J=6.3 Hz, 2H), 3.08 (t, J=7.4 Hz, 2H), 1.93-2.04 (m, 2H), 1.73-1.84 (m, 4H), 1.47-1.55 (m, 8H), 1.26-1.41 (m, 8H), 0.88-0.93 (m, 3H)			
75			350.1
^{1}H NMR (500 MHz , CD_3OD) δ 6.94-6.98 (m, 2H), 6.88-6.92 (m, 1H), 4.05 (s, 4H), 3.32 (s, 2H), 3.11 (t, J=7.2 Hz, 2H), 1.94-2.04 (m, 2H), 1.73-1.86 (m, 4H), 1.27-1.45 (m, 10H), 0.88-0.95 (m, 3H)			

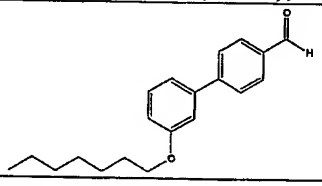
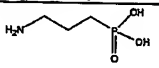
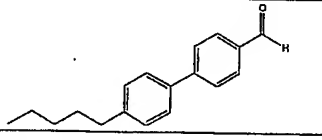
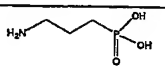
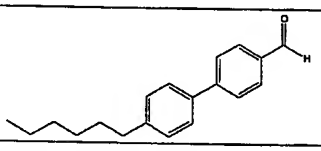
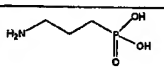
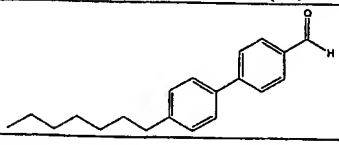
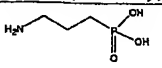
76			496.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.31 (s, 1H), 7.18 (s, 1H), 4.12 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.15 (t, J=7.1 Hz, 2H), 1.96-2.06 (m, 2H), 1.73-1.82 (m, 4H), 1.49-1.56 (m, 2H), 1.27-1.42 (m, 12H), 0.89-0.94 (m, 3H)			
77			438.0
^{1}H NMR (500 MHz , CD_3OD) δ 7.31 (s, 1H), 7.18 (s, 1H), 4.12 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.12-3.17 (t, 2H), 1.96-2.06 (m, 2H), 1.73-1.82 (m, 4H), 1.48-1.57 (m, 2H), 1.34-1.41 (m, 4H), 0.91-0.97 (m, 3H)			
78			510.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.31 (s, 1H), 7.18 (s, 1H), 4.11 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.11-3.17 (t, 2H), 1.95-2.06 (m, 2H), 1.71-1.81 (m, 4H), 1.48-1.56 (m, 2H), 1.27-1.42 (m, 14H), 0.88-0.94 (m, 3H)			
79			302.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.31-7.40 (m, 2H), 7.02-7.08 (m, 2H), 4.12 (s, 2H), 4.03 (t, J=6.4 Hz, 2H), 3.12 (t, J=6.4 Hz, 2H), 1.94-2.04 (m, 2H), 1.66-1.81 (m, 4H), 1.48-1.56 (m, 2H), 0.97-1.02 (m, 3H)			
80			442.2

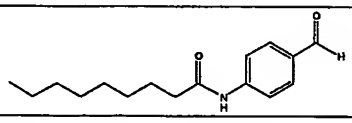
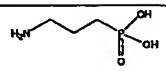
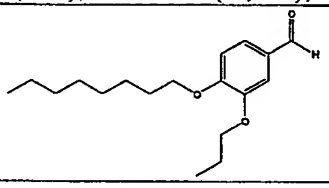
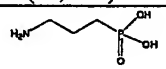
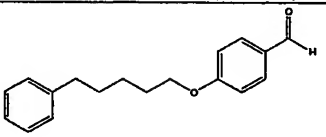
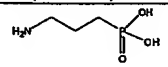
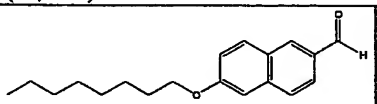
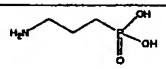
^{1}H NMR (500 MHz , CD_3OD) δ 7.43 (d, J=7.5 Hz, 4H), 7.38 (t, J=7.5 Hz, 4H), 7.33 (d, J=7.1 Hz, 2H), 6.76 (s, 2H), 6.71 (s, 1H), 5.10 (s, 4H), 4.08 (s, 2H), 3.08 (t, J=6.4 Hz, 2H), 1.93-2.04 (m, 2H), 1.68-1.76 (m, 2H)			
81			402.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.98 (s, 1H), 6.90 (s, 1H), 4.10 (s, 2H), 3.94 (t, J=6.6 Hz, 2H), 3.88 (s, 3H), 3.14 (t, J=7.7 Hz, 2H), 2.27 (s, 3H), 1.96-2.06 (m, 2H), 1.71-1.85 (m, 4H), 1.46-1.54 (m, 2H), 1.28-1.42 (m, 8H), 0.90-0.95 (m, 3H)			
82			464.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.52 (d, J=7.4 Hz, 2H), 7.42 (t, J=7.4 Hz, 2H), 7.36 (t, J=7.3 Hz, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 4.20 (s, 2H), 3.95 (s, 3H), 3.71 (t, J=6.3 Hz, 2H), 3.36 (s, 2H), 3.19 (t, J=7.5 Hz, 2H), 1.98-2.09 (m, 2H), 1.78-1.87 (m, 2H), 1.41-1.48 (m, 2H), 1.25-1.34 (m, 2H), 1.08-1.25 (m, 6H), 0.87-0.94 (m, 3H)			
83			374.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.94-6.98 (m, 2H), 6.88-6.92 (m, 1H), 4.05 (s, 4H), 3.32 (s, 2H), 3.11 (t, J=7.2 Hz, 2H), 1.94-2.04 (m, 2H), 1.73-1.86 (m, 4H), 1.27-1.45 (m, 10H), 0.88-0.95 (m, 3H)			
84			392.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.69 (d, J=8.0, 2H), 7.57 (d, J=8.7 Hz, 2H), 7.54 (d, J=8.0 Hz, 2H), 7.01 (d, J=8.5 Hz, 2H), 4.22 (s, 2H), 4.03 (t, 2H), 3.18 (t, 2H), 1.98-2.08 (m, 2H), 1.76-1.86 (m, 4H), 1.40-1.53 (m, 4H), 0.96-1.00 (m, 3H)			
85			378.1

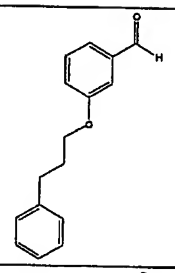
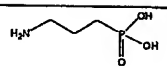
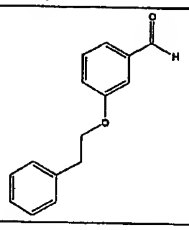
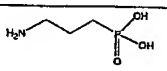
^{1}H NMR (500 MHz , CD_3OD) δ 7.70 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 7.55 (d, J=7.55 Hz, 2H), 7.02 (d, J=8.7 Hz, 2H), 4.24 (s, 2H), 4.05 (t, J=6.4 Hz, 2H), 3.20 (t, J=7.6 Hz, 2H), 1.99-2.10 (m, 2H), 1.76-1.88 (m, 4H), 1.51-1.59 (m, 2H), 1.00-1.08 (m, 3H)			
86			406.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.70 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 7.55 (d, J=8.3 Hz, 2H), 7.02 (d, J=8.4 Hz, 2H), 4.24 (s, 2H), 4.04 (t, J=6.4 Hz, 2H), 3.16-3.23 (t, 2H), 1.99-2.10 (m, 2H), 1.76-1.88 (m, 4H), 1.48-1.58 (m, 2H), 1.36-1.45 (m, 4H), 0.91-1.00 (m, 3H)			
87			468.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.69 (d, J=8.0 Hz, 2H), 7.67 (s, 1H), 7.56 (d, J=8.2 Hz, 2H), 7.15 (d, J=8.5 Hz, 2H), 4.24 (s, 2H), 4.11 (t, J=6.1 Hz, 2H), 3.19 (t, J=7.2 Hz, 2H), 1.98-2.08 (m, 2H), 1.78-1.88 (m, 4H), 1.51-1.59 (m, 2H), 1.29-1.46 (m, 8H), 0.88-0.96 (m, 3H)			
88			434.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.68 (d, J=8.2 Hz, 2H), 7.54 (d, J=8.2 Hz, 2H), 7.30 (s, 2H), 4.24 (s, 2H), 3.83 (t, J=6.5 Hz, 2H), 3.19 (t, J=7.4 Hz, 2H), 2.34 (s, 6H), 2.00-2.09 (m, 2H), 1.78-1.88 (m, 4H), 1.54-1.62 (m, 2H), 1.38-1.46 (m, 4H), 0.94-1.01 (m, 3H)			
89			440.1

^{1}H NMR (500 MHz , CD_3OD) δ 7.70 (d, J=8.0 Hz, 2H), 7.68 (s, 1H), 7.57 (d, J=8.0 Hz, 3H), 7.16 (d, J=8.5 Hz, 1H), 4.25 (s, 2H), 4.12 (t, J=6.3 Hz, 2H), 3.20 (t, J=7.5 Hz, 2H), 2.00-2.09 (m, 2H), 1.80-1.90 (m, 4H), 1.53-1.61 (m, 2H), 1.38-1.46 (m, 4H), 0.93-0.99 (m, 3H)			
90			
^{1}H NMR (500 MHz , CD_3OD) δ 7.57 (d, J=8.0 Hz, 2H), 7.24 (d, J=7.8 Hz, 2H), 6.67 (s, 2H), 4.25 (s, 2H), 3.94-4.00 (t, 2H), 3.18-3.25 (t, 2H), 2.00-2.05 (m, 2H), 1.99 (s, 6H), 1.78-1.90 (m, 4H), 1.45-1.55 (m, 2H), 1.35-1.40 (m, 4H), 0.95-1.00 (m, 3H)			
91			454.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.68 (d, J=8.0 Hz, 2H), 7.57 (d, J=7.57, 2H), 7.51 (s, 1H), 7.43 (s, 1H), 4.22 (s, 2H), 3.97 (t, J=6.3 Hz, 2H), 3.14-3.22 (t, 2H), 2.38 (s, 3H), 1.98-2.08 (m, 2H), 1.74-1.88 (m, 4H), 1.54-1.62 (m, 2H), 1.36-1.46 (m, 4H), 0.92-1.00 (m, 3H)			
92			436.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.71 (d, J=8.0 Hz, 2H), 7.54 (d, J=8.3 Hz, 2H), 7.20-7.23 (m, 1H), 7.18-7.20 (m, 1H), 7.04 (d, J=8.5 Hz, 1H), 4.24 (s, 2H), 4.05 (t, J=6.5 Hz, 2H), 3.92 (s, 3H), 3.19 (t, J=7.4 Hz, 2H), 2.00-2.08 (m, 2H), 1.78-1.88 (m, 4H), 1.48-1.56 (m, 2H), 1.36-1.43 (m, 4H), 0.92-0.98 (m, 3H)			
93			

^{1}H NMR (500 MHz , CD_3OD) δ 7.71 (d, J=8.1 Hz, 2H), 7.57 (d, J=7.5 Hz, 2H), 7.32-7.39 (m, 1H), 7.10-7.21 (m, 2H), 6.90-6.96 (m, 1H), 4.16-4.25 (m, 2H), 4.00-4.08 (m, 2H), 3.12-3.22 (m, 2H), 1.96-2.06 (m, 2H), 1.72-1.84 (m, 2H), 1.62-1.72 (m, 2H), 1.50-1.60 (m, 2H), 1.38-1.48 (m, 2H), 0.98-1.06 (m, 3H)			
94			302.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.69-7.74 (m, 2H), 7.57 (d, J=7.6 Hz, 2H), 7.32-7.39 (m, 1H), 7.19 (d, J=7.1 Hz, 1H), 7.15 (s, 1H), 6.94 (d, J=8.0 Hz, 1H), 4.25 (s, 2H), 4.03-4.05 (m, 2H), 3.18-3.21 (m, 2H), 1.97-2.09 (m, 2H), 1.76-1.88 (m, 4H), 1.46-1.54 (m, 2H), 1.38-1.46 (m, 2H), 0.94-1.00 (m, 3H)			
95			406.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.73 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.2 Hz, 2H), 7.38 (t, J=7.9 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.16 (s, 1H), 6.90 (d, J=6.0 Hz, 1H), 4.26 (s, 2H), 4.05 (t, J=6.4 Hz, 2H), 3.21 (t, J=7.5 Hz, 2H), 2.00-2.10 (m, 2H), 1.78-1.88 (m, 4H), 1.50-1.56 (m,, 2H), 1.36-1.44 (m, 4H), 0.92-0.98 (m, 3H)			
96			382.0
^{1}H NMR (500 MHz , CD_3OD) δ 7.87 (s, 1H), 7.82 (d, J=7.7 Hz, 2H), 7.69 (d, J=7.8 Hz, 2H), 7.59-7.67 (m, 4H), 7.54-7.59 (m, 1H), 7.49 (t, J=7.6 Hz, 2H), 7.36-7.42 (m, 1H), 4.29 (s, 2H), 3.22 (t, J=7.6 Hz, 2H), 2.00-2.12 (m, 2H), 1.80-1.90 (m, 2H)			
97			382.0

^{1}H NMR (500 MHz , CD_3OD) δ 7.45-7.48 (m, 2H), 7.40-7.45 (m, 2H), 7.36 (d, J=8.1 Hz, 2H), 7.25 (d, J=8.3 Hz, 2H), 7.18-7.22 (m, 3H), 7.11-7.15 (m, 2H), 4.17 (s, 2H), 3.14 (t, J=7.6 Hz, 2H), 1.99-2.01 (m, 2H), 1.95-1.97 (m, 2H)			
98			420.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (d, J=8.0 Hz, 2H), 7.57 (d, J=8.0 Hz, 2H), 7.34-7.39 (t, 1H), 7.18-7.22 (d, 1H), 7.15 (s, 1H), 6.92-6.96 (d, 1H), 4.25 (s, 2H), 4.04 (t, J=6.4 Hz, 2H), 3.19 (t, J=7.5 Hz, 2H), 1.98-2.08 (m, 2H), 1.76-1.86 (m, 4H), 1.47-1.55 (m, 2H), 1.31-1.45 (m, 6H), 0.90-0.96 (m, 3H)			
99			376.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (d, J=8.3 Hz, 2H), 7.56 (d, J=8.0 Hz, 4H), 7.29 (d, J=8.0 Hz, 2H), 4.24 (s, 2H), 3.19 (t, J=7.6 Hz, 2H), 2.66 (t, J=7.6 Hz, 2H), 2.00-2.09 (m, 2H), 1.79-1.87 (m, 2H), 1.63-1.70 (m, 2H), 1.28-1.41 (m, 4H), 0.89-0.96 (m, 3H)			
100			390.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (d, J=8.0 Hz, 2H), 7.56 (d, J=7.8 Hz, 4H), 7.29 (d, J=8.0 Hz, 2H), 4.25 (s, 2H), 3.19 (t, J=7.5 Ha, 2H), 2.67 (t, J=7.7, 2H), 2.00-2.09 (m, 2H), 1.78-1.87 (m, 2H), 1.61-1.70 (m, 2H), 1.31-1.41 (m, 6H), 0.98-0.94 (m, 3H)			
101			404.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.73 (d, J=8.0 Hz, 2H), 7.57 (d, J=7.6 Hz, 2H), 7.30 (d, J=8.3 Hz, 4H), 4.26 (s, 2H), 3.20 (t, J=7.6 Hz, 2H), 2.68 (t, J=7.7 Hz, 2H), 2.00-2.10 (m, 2H0, 1.80-1.88 (m, 2H), 1.64-1.70 (m, 2H), 1.26-1.40 (m, 8H), 0.90-0.95 (m, 3H)			

102			330.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.37 (t, J=8.0 Hz, 1H), 6.99-7.07 (m, 3H), 4.16 (s, 2H), 4.02 (t, J=6.6 Hz, 2H), 3.15 (t, J=7.6 Hz, 2H), 1.96-2.06 (m, 2H), 1.75-1.84 (m, 4H), 1.46-1.54 (m, 2H), 1.34-1.46 (m, 8H), 0.91-0.97 (m, 3H)			
103			416.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.07 (s, 1H), 6.99 (s, 2H), 4.09 (s, 2H), 4.03 (t, J=6.3 Hz, 2H), 3.97 (t, J=6.3 Hz, 2H), 3.11 (J=7.1 Hz, 2H), 1.93-2.04 (m, 2H), 1.72-1.84 (m, 6H), 1.46-1.54 (m, 2H), 1.26-1.42 (m, 8H), 1.02-1.08 (m, 3H), 0.86-0.94 (m, 3H)			
104			392.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.4 Hz, 2H), 7.25 (t, J=7.5 Hz, 2H), 7.12-7.19 (m, 3H), 6.98 (d, J=8.7 Hz, 2H), 4.12 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.13 (t, J=7.5 Hz, 2H), 2.65 (t, J=7.6 Hz, 2H), 1.94 (m, 2H), 1.74-1.86 (m, 4H), 1.66-1.74 (m, 2H), 1.48-1.56 (m, 2H)			
105			408.4
^{1}H NMR (500 MHz , CD_3OD) δ 7.91 (s, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.82 (d, J=8.9 Hz, 1H), 7.51 (d, J=8.5 Hz, 1H), 7.27 (s, 1H), 7.21 (d, J=8.8 Hz, 1H), 4.32 (s, 2H), 4.11 (t, J=6.3 Hz, 2H), 3.16-3.22 (m, 2H), 1.98-2.08 (m, 2H), 1.76-1.90 (m, 4H), 1.48-1.58 (m, 2H), 1.28-1.46 (m, 8H), 0.90-0.96 (m, 3H)			

106			440.4
107			426.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.71 (d, J=7.8 Hz, 2H), 7.56 (d, J=8.0, 2H), 7.28-7.39 (m, 5H), 7.18-7.25 (m, 2H), 7.14 (s, 1H), 6.95 (d, J=8.0 Hz, 1H), 4.22-4.31 (m, 4H),.3.19 (d, J=7.4 Hz, 2H), 3.11 (d, J=6.6 Hz, 2H), 1.97-2.09 (m, 2H), 1.78-1.88 (m, 2H)			

EXAMPLE 108

(R/S)-3-(N-(4-Nonylbenzyl)amino-1-hydroxypropylphosphonic acid

Step A: (R/S)-Diethyl 3-benzyloxycarbonylamino-1-hydroxypropylphosphonate

To a solution of potassium bis(trimethylsilyl)amide (1.13g, 5.66 mmol) in tetrahydrofuran (10 mL) at 0 °C was added diethyl phosphite (0.73 g, 5.66 mmol). After 10 min, 3-(benzyloxycarbonylamino)propanal (0.78 g, 3.77 mmol) was added as a solution in tetrahydrofuran (5 mL). After 30 min, the reaction was quenched by the addition of 2N hydrochloric acid (25 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with hexane/acetone (1:1) gave a colorless oil (0.36 g): ESI-MS 346.1 (M+H).

Step B: (R/S)-Diethyl 3-amino-1-hydroxypropylphosphonate

(R/S)-Diethyl 3-benzyloxycarbonylamino-1-hydroxypropylphosphonate (0.36 g, 1.04 mmol, from Step A) and palladium on carbon (10%, 0.10 g) were stirred together in methanol (5 mL) under an atmosphere of

hydrogen. After 2 h, the reaction was filtered and concentrated *in vacuo* to give a colorless oil: ^{1}H NMR (500 MHz , CD_3OD) δ 4.10-4.22 (m, 4H), 4.00-4.05 (m, 1H), 2.85-3.00 (m, 2H), 1.85-2.00 (m, 2H), 1.34 (t, J=7.0 Hz, 6H); ESI-MS 211.8 (M+H)

Step: C (R/S)-Diethyl 3-(N-(4-nonylbenzyl)amino-1-hydroxypropylphosphonate

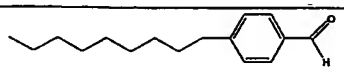
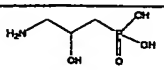
(R/S)-Diethyl 3-amino-1-hydroxypropylphosphonate (0.030 g, 0.142 mmol, from Step C), 4-nonylbenzaldehyde (0.036 g, 0.142 mmol) and sodium cyanoborohydride (0.004 g, 0.071 mmol) in methanol (1.5 mL) were heated at 50°C for 3 h. The reaction was made acidic (pH~5) by the addition of concentrated hydrochloric acid then directly purified by LC-3 to give a colorless oil (0.031 g).

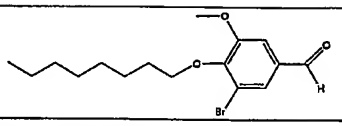
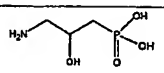
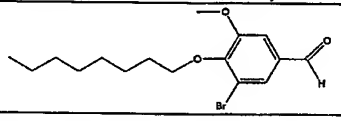
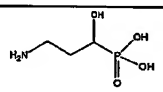
Step D: (R/S)-3-(N-(4-nonylbenzyl)amino-1-hydroxypropylphosphonic acid

(R/S)-Diethyl 3-(N-(4-nonylbenzyl)amino-1-hydroxypropylphosphonate (0.031 g) was dissolved in acetonitrile (1 mL) and treated with bromotrimethylsilane (0.050 mL, 0.362 mmol). After stirring for 1 h at 50°C, the reaction was quenched with methanol (1 mL), stirred for 30 min then concentrated. The residue was purified via HPLC to give desired product (0.011 g): ^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 4.16 (s, 2H), 3.87-3.92 (m, 1H), 3.18-3.34 (m, 2H), 2.64 (t, J=7.7 Hz, 2H), 2.04-2.20 (m, 2H), 1.58-1.64 (m, 2H), 1.24-1.34 (m, 12H), 0.89 (t, J=7.0 Hz, 3H); ESI-MS 372.2 (M+H).

EXAMPLES 109-111

The following EXAMPLES (109-111) were made according to the procedure described for EXAMPLE 108 substituting A for 4-nonylbenzaldehyde and the diethyl ester of B for (R/S)-diethyl 3-amino-1-hydroxyphosphonate in Step C.

EXAMPLE	A	B	ESI-MS
109			372.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.42 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 4.24-4.50 (m, 1H), 4.21 (s, 2H), 3.30-3.38 (m, 1H), 3.01 (dd, J=12.8, 9.6 Hz, 1H), 2.67 (t, J=7.7 Hz, 2H), 1.94-2.14 (m, 2H), 1.60-1.68 (m, 2H), 1.26-1.38 (m, 12H), 0.92 (t, J=7.0 Hz, 3H)			

110			482.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.33 (d, J=1.9 Hz, 1H), 7.19 (d, J=1.8 Hz, 1H), 4.22-4.28 (m, 1H), 4.18 (s, 2H), 4.01 (t, J=6.4 Hz, 2H), 3.93 (s, 3H), 3.30-3.35 (m, 1H), 3.03 (dd, J=12.6, 8.7 Hz, 1H), 1.91-2.11 (m, 2H), 1.75-1.82 (m, 2H), 1.50-1.58 (m, 2H), 1.30-1.42 (m, 8H), 0.93 (t, J=7.0 Hz, 3H)			
111			482.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.33 (d, J=2.1 Hz, 1H), 7.19 (d, J=1.8 Hz, 1H), 4.18 (s, 2H), 4.02 (t, J=6.4 Hz, 2H), 3.92-3.96 (m, 1H), 3.93 (s, 3H), 3.23-3.36 (m, 2H), 2.08-2.26 (m, 2H), 1.75-1.82 (m, 2H), 1.50-1.58 (m, 2H), 1.30-1.42 (m, 8H), 0.93 (t, J=7.0 Hz, 3H)			

EXAMPLE 112

N-(4-Nonylbenzyl)-3-aminopropylphosphonic acid

3-Aminopropylphosphonic acid (0.060 g, 0.436 mmol) and tetrabutylammonium hydroxide (1.0M in methanol, 0.44 mL, 0.43 mmol) in methanol (3 mL) were heated at 50°C for 15 min until all of the solids had dissolved. 4-(Nonyl)benzyliodide (0.100 g, 0.291 mmol) and DIEA (0.112 g, 0.872 mmol) were added and stirring was continued for 12 h at 50 °C. The reaction was made acidic (pH~5) by the addition of concentrated hydrochloric acid then directly purified using LC-3 to give the title compound (0.020 g): ^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.14 (t, J=7.6 Hz, 2H), 2.64 (t, J=7.7 Hz, 2H), 2.00 (m, 2H), 1.79 (td, J=5.3, 18.5 Hz, 2H), 1.61 (m, 2H), 1.24-1.36 (m, 14H), 0.89 (t, J=7.0 Hz, 3H); ESI-MS 356.2 (M+H).

EXAMPLE 113

3-[(4-Octylbenzyl)amino]propylphosphinic acid

Step A: Ethyl 2-cyanoethyl(diethoxymethyl)phosphinate

To a solution 2.6234 g (13.37 mmol) of ethyldiethoxymethyl phosphinate in 10 mL EtOH was added 0.5670 g (10.70 mmol) acrylonitrile. The resulting mixture was added to a solution of 0.071 g (2.81 mmol) NaH in 10 mL EtOH at 0 °C. The ice bath was removed at the end of the addition, and the reaction mixture was stirred at rt for 16 hr. The mixture was neutralized (pH = 7) with HOAc, and was partitioned between EtOAc and H_2O. The organic layer was separated, dried and concentrated, which provided 2.47 g (93% yield) of the title compound: ^{1}H NMR (500 MHz) δ 1.25 (t, J = 6.9, 6H), 1.34 (t, J = 7.1, 3H), 2.11-2.19 (m, 2H), 2.68-2.74 (m, 2H), 3.62-3.73 (m, 2H), 3.80-3.87 (m, 2H), 4.13-4.25 (m, 2H), 4.70 (d, J = 6.4, 1H); ESI-MS 250 (M+H).

Step B: Ethyl 3-Aminopropyl(diethoxymethyl)phosphinate

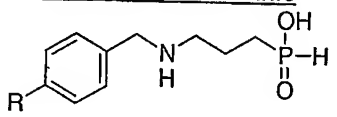
To a solution of 2.47 g (9.91 mmol) of ethyl 2-cyanoethyl (diethoxymethyl)phosphinate (from Step A) in 20 mL 2.0 M ammonia in EtOH was added 250 mg Raney Nickel. The mixture was subjected to hydrogenation conditions (H_2, 40 psi, rt) for 16 hr. The reaction mixture was filtered over Celite and partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted twice with CH_2CL_2. The organic layer and extractions were combined, dried, and concentrated to provide 2.13 g (85% yield) of the title compound: ^{1}H NMR (500 MHz) δ 1.23 (dt, J_1 = 7.1, J_2 = 1.6 6H), 1.29 (t, J = 7.1, 3H), 1.42 (s, br, 2H), 1.71-1.82 (m, 4H), 2.72-2.75 (m, 2H), 3.63-3.70 (m, 2H), 3.78-3.86 (m, 2H), 4.08-4.21 (m, 2H), 4.64 (d, J = 6.7, 1H); ESI-MS 254 (M+H).

Step C: 3-[(4-Octylbenzyl)amino]propylphosphinic acid

A mixture of 98.5 mg (0.389 mmol) of ethyl 3-aminopropyl (diethoxymethyl)phosphinate (from Step B) and 84.9 mg (0.389 mmol) of 4-octylbenzaldehyde in 1 mL of MeOH at rt was treated with 12.2 mg (0.194 mmol) $Na(CN)BH_3$. The resulting reaction mixture was stirred at rt for 16 hr. The reaction was quenched with 0.5 mL of 12 N HCl, then heated up to 80 °C for 1 hr. The mixture was cooled and concentrated. HPLC purification (LC-2) afforded 60 mg (47%) of the title compound: ^{1}H NMR (500 MHz, CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.25-1.33 (m, 10H), 1.59-1.66 (m, 4H), 1.90-1.96 (m, 2H), 2.63 (t, J = 7.7, 2H), 3.09 (t, J = 6.9, 2H),

4.12 (s, 2H), 7.03 (d, J = 505.6, 1H), 7.27 (d, J = 8.0, 2H), 7.38 (d, J = 8.0, 2H); LC-1: 3.02 min; ESI-MS 326 (M+H).

EXAMPLES 114-116



The following compounds were prepared using procedures analogous to those described in EXAMPLE 113 substituting the appropriate Aldehyde for 4-octylbenzaldehyde in Step C.

EXAMPLE	R	LC-1 (min)	ESI-MS (M+H)
114	$CH_3(CH_2)_8$-	3.00	340
115	$CH_3(CH_2)_8O$-	2.93	356
116	$CH_3(CH_2)_9$-	3.23	354

EXAMPLE 117

3-(N-(4-(4'-Pentyl)biphenylmethyl))aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 56 for 4-octylbenzaldehyde in Step C: LC-1: 2.86 min; ESI-MS 360 (M+H).

EXAMPLE 118

3-(N-(4-(4'-Heptyloxy)biphenylmethyl))aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 51 for 4-octylbenzaldehyde in Step C: LC-1: 3.06 min; ESI-MS 404 (M+H).

EXAMPLE 119

3-N-(3-Bromo-5-methoxy-4-(octyloxy)benzyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 13 for 4-octylbenzaldehyde in Step C: LC-1: 2.98 min; ESI-MS 450 (M+H).

EXAMPLE 120

3-N-(3-Fluoro-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting 3-fluoro-4-(nonyloxy)benzaldehyde for 4-octylbenzaldehyde in Step C: ^{1}H NMR (500 Mhz) δ 0.91 (t, *J*=7.0, 3H), 1.30-1.40 (m, 10H), 1.48-1.51 (m, 2H), 1.71-1.99 (m, 6H), 3.11 (t, *J*=7.2, 2H), 4.07 (t, *J*=6.4, 2H), 4.12 (s, 2H), 7.06 (d, *J*=519, 1H), 7.13-7.29 (m, 3H); LC-1: 2.96 min; ESI-MS 374 (M+H).

EXAMPLE 121

3-N-(2-Chloro-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting 2-chloro-4-(nonyloxy)benzaldehyde for 4-octylbenzaldehyde in Step C: LC-1 : 3.07 min; ESI-MS 390 (M+H).

EXAMPLE 122

3-N-(6-Heptyloxy)napthylmethyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting 6-heptyloxy-1-napthaldehyde for 4-octylbenzaldehyde in Step C: LC-1: 2.90 min; ESI-MS 378 (M+H).

EXAMPLE 123

3-(N-(3-Cyclopropyloxy-4-(nonyloxy)benzyl)amino)propylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 77 for 4-octylbenzaldehyde in Step C: LC-1: 3.04 min; ESI-MS 412 (M+H).

EXAMPLE 124

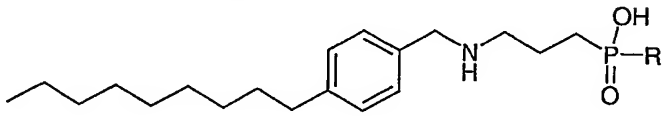
3-(N-(4-(Nonylthio)benzyl)amino)propylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 78 for 4-octylbenzaldehyde in Step C: ^{1}H NMR (500 Mhz) (CD_3OD) δ 0.90 (t, J = 7.0, 3H), 1.30-1.32 (m, 10H), 1.43-1.46 (m, 2H), 1.63-1.66 (m, 2H), 1.78-1.83 (m, 2H), 1.95-1.99 (m, 2H), 2.98 (t, J = 7.2, 2H), 3.14 (t, J = 7.5, 2H), 4.16 (s, 2H), 7.08 (d, J = 533, 1H), 7.37-7.42 (m, 4H); LC-1: 3.10 min; ESI-MS 372 (M+H).

EXAMPLE 125

Ethyl (3-(4-nonylbenzyl)amino)propylphosphinic acid A solution of 88 mg (0.26 mmol) of 3-((4-nonylbenzyl)amino)propylphosphinic acid (from EXAMPLE 114) in 1 mL N,N-bis(trimethylsilyl)amine was heated to 100 °C for 8 hr. Upon cooling to rt, 81.1 mg (0.52 mmol) of iodoethane was added, followed by the addition of 67.2 mg (0.52 mmol) of DIEA. The resulting mixture was heated to 60 °C overnight. The reaction mixture was cooled and concentrated. HPLC purification (LC-2) afforded 12 mg (13%) of the title compound. ^{1}H NMR (500 MHz) (CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.09-1.18 (m, 3H), 1.26-1.31 (m, 12H), 1.59-1.75 (m, 6H), 1.94-2.00 (m, 2H), 2.63 (t, J = 7.6, 2H), 3.10 (t, J = 6.9, 2H), 4.13 (s, 2H), 7.27 (d, J = 8.0, 2H), 7.39 (d, J = 8.0 2H); LC-1: 2.92 min; ESI-MS 368 (M+H).

EXAMPLES 126-127



The following compounds were prepared a procedure analogous to that described in EXAMPLE 125 substituting the appropriate alkyl halide for ethyl iodide.

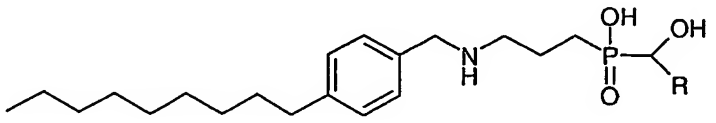
EXAMPLE	R	LC-1 (min)	ESI-MS (M+H)
126	$CH_3CH_2CH_2$-	3.03	382
127	$PhCH_2$-	3.41	430

EXAMPLE 128

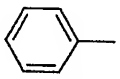
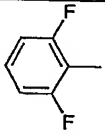
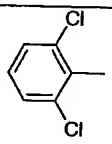
Hydroxymethyl (3-(4-nonylbenzyl)amino)propylphosphinic acid

A solution of 71 mg (0.21 mmol) of 3-(4-nonylbenzyl)aminopropylphosphinic acid (from EXAMPLE 114) in 1 mL of N,N-(trimethylsilyl)amine was heated to 100 °C for 8 hr. Upon cooling to rt, 15.8 mg (0.53 mmol) of paraformaldehyde was added. The resulting mixture was heated at 30 °C for 3 hr, and stirred at rt under nitrogen for 16 hr. The reaction mixture concentrated. HPLC purification (LC-2) afforded 22 mg (28%) of the title compound. ^{1}H NMR (500 MHz) (CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.27-1.31 (m, 12H), 1.57-1.63 (m, 2H), 1.80-1.85 (m, 2H); 1.97-2.05 (m, 2H), 2.63 (t, J = 7.8, 2H), 3.12 (t, J = 6.9, 2H), 3.70 (d, J = 6.2, 2H), 4.13 (s, 2H), 7.27 (d, J = 8.0, 2H), 7.39 (d, J = 8.2, 2H); LC-1: 2.90 min; ESI-MS 370 (M+H).

EXAMPLES 129-133



The following compounds were prepared using a procedure analogous to that described in EXAMPLE 128 substituting the appropriate aldehyde for paraformaldehyde.

EXAMPLE	R	LC-1 (min)	ESI-MS (M+H)
129	CH_3-	2.89	384
130	CH_3CH_2-	2.95	398
131		3.26	446
132		3.25	482
133		3.45	514

EXAMPLE 134

Hydroxymethyl (3-(4-octylbenzyl)amino)propylphosphinic acid

The title compound was prepared from 3-(4-octylbenzyl)aminopropylphosphinic acid (from EXAMPLE 114) using a procedure analogous to that described in EXAMPLE 128: LC-1: 2.67 min; ESI-MS 356 (M+H).

EXAMPLE 135

Hydroxymethyl 3-(3-(cyclopropyloxy)-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was prepared from 3-(3-(cyclopropyloxy)-4-(nonyloxy)benzyl)aminopropylphosphinic acid (from EXAMPLE 123) using a procedure analogous to that described in EXAMPLE 128: LC-1: 2.95 min; ESI-MS 442 (M+H).

EXAMPLE 136

Hydroxymethyl 3-(3-fluoro-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was prepared from 3-(3-fluoro-4-(nonyloxy)benzyl)amino-propylphosphinic acid (from EXAMPLE 125) using a procedure analogous to that described in EXAMPLE 128: LC-1: 2.87 min; ESI-MS 404 (M+H).

EXAMPLE 137

Ethoxycarbonyl 3-(N-(4-(4'-heptyloxy)biphenylmethyl))aminopropylphosphinic acid

To a solution of 32.5 mg (0.081 mmol) of 3-(N-(4-(4'-heptyloxy)biphenylmethyl)) aminopropylphosphinic acid (from EXAMPLE 118) in 2 mL dichloromethane was added 0.1 mL of TMSCl and 0.12 mL of DIEA at 0 °C. The solution was stirred at rt for an additional one hour and 0.1 mL of ethyl chloroformate (0.81 mmol) was added. The reaction was quenched with MeOH and concentrated to oil. The product was isolated and purified by LC-2: ^{1}H NMR (500 Mhz) (CD_3OD) δ 0.94 (t, J = 6.9, 3H), 1.31-1.43 (m, 8H), 1.51-1.53 (m, 2H), 1.80-1.83 (m, 2H), 1.89-1.92 (m, 2H), 2.03-2.06 (m, 2H), 3.18 (t, J = 6.7, 2H), 4.05 (t, J = 6.4, 2H), 4.24 (s, 2H), 4.25 (q, J =7.0, 2H), 6.95-7.72 (m, 8H); LC-1: 3.26 min; ESI-MS 476 (M+H).

EXAMPLE 138

3-(4-Octylbenzyl)amino-2-phenylpropylphosphinic acid

A mixture of 69.2 mg (0.210 mmol) of ethyl 3-amino-2-phenylpropyl(diethoxymethyl)phosphinate (*Tetrahedron*, **1989**, 3787-3808) and 48.2 mg (0.221 mmol) of 4-octylbenzaldehyde in 1 mL of MeOH at rt was treated with 6.7 mg (0.105 mmol) of $Na(CN)BH_3$. The resulting reaction mixture was stirred at rt for 16 hr. The reaction was quenched with 0.3 mL of 12 N HCl, then heated up to 60 °C for 5 hr. The mixture was cooled and concentrated. HPLC purification (LC-2) afforded 22 mg (26%) of the title compound. ^1H NMR (500 MHz) (CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.26-1.30 (m, 10H), 1.58-1.61 (m, 2H), 2.01-2.17 (m, 2H), 2.62 (t, J = 7.8, 2H), 3.20-3.23 (m, 1H),3.35-3.46 (m, 2H), 4.11 (s, 2H), 6.92 (d, J = 525.4, 1H), 7.23-7.37 (m, 9H); LC-1: 3.31 min; ESI-MS 402 (M+H).

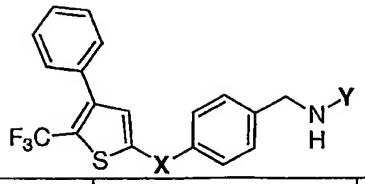
EXAMPLE 139

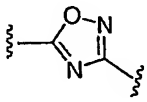
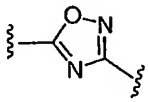
3-(3-Bromo-5-methoxy-4-(octyloxy)benzyl)amino-2-phenylpropylphosphinic acid

The title compound was prepared using a procedure analogous to that described in EXAMPLE 138 substituting Aldehyde 13 for 4-octylbenzaldehyde: LC-1: 3.51 min; ESI-MS 526 (M+H).

EXAMPLES 140-150

The following compounds were prepared using a procedure analogous to that described in EXAMPLE 1 substituting the appropriate aminoalkylcarboxylic acid or aminoalkylphosphonic acid for 3-aminopropylphosphonic acid and either Aldehyde 79 or 80 for 4-(decyloxy)benzaldehyde. The products were purified using LC-2.



EXAMPLE	X	Y	LC-1 (min)	ESI-MS (M+H)
140		-$(CH_2)_3PO_3H_2$	3.01	524
141		-$(CH_2)_3CO_2H$	3.07	448
142	-CH_2O-	-$(CH_2)_3PO_3H_2$	2.77	486
143	-CH_2O-	-$(CH_2)_3CO_2H$	2.79	450
144	-CH_2O-	-$(CH_2)_2CO_2H$	2.72	436
145	-CH_2O-	-$CH_2CH(CH_3)CO_2H$	3.00	450
146	-CH_2O-	-$CH_2CH(OH)CO_2H$		
147	-CH_2O-	-CH(n-Pr)CH_2CO_2H	3.11	478

^{1}H NMR (500 MHz, CD_3OD) δ 0.97 (3H, t, J=7.3); 1.29-1.51 (2H, m); 1.63-1.71 (1H, m); 1.78-1.84 (1H, m); 2.66-2.83 (3H, m); 3.46-3.54 (1H, m); 4.23 (2H, s); 5.38 (2H, s); 7.12 (2H, d, J=8.5); 7.21 (1H, s); 7.41-7.44 (5H, m); 7.47 (2H, d, J=8.5)				
148	$-CH_2O-$	$-CH(i\text{-}Pr)CH_2CO_2H$	3.06	478
^{1}H NMR (500 MHz, CD_3OD) δ 0.97 (3H, d, J=6.8); 1.01 (3H, d, J=6.8); 2.15-2.21 (1H, m); 2.66-2.83 (3H, m); 3.48-3.51 (1H, m); 4.28 (2H, q, J=13 & 28); 5.39 (2H, s); 7.13 (2H, d, J=8.5); 7.21 (1H, s); 7.42-7.47 (5H, m); 7.49 (2H, d, J=8.5)				
149	$-CH_2O-$	$-CH(CH_3)CH_2CO_2H$	2.90	450
^{1}H NMR (500 MHz, CD_3OD) δ 1.42 (3H, d, J=6.6); 2.66-2.79 (2H, m); 2.83 (1H, s); 3.59-3.64 (1H, m); 4.21 (2H, q, J=13 & 28); 5.38 (2H, s); 7.13 (2H, d, J=8.4); 7.21 (1H, s); 7.42-7.45 (5H, m); 7.47 (2H, d, J=8.4)				
150	$-CH_2O-$	$-(CH_2)_4CO_2H$	2.95	464
^{1}H NMR (500 MHz, CD_3OD) δ 1.60-1.80 (4H, m); 2.30-2.50 (2H, m); 3.24 (2H, s); 4.53 (2H, s); 5.31 (2H, s); 7.13 (2H, d, J=8.4); 7.21 (1H, s); 7.42-7.45 (5H, m); 7.47 (2H, d, J=8.4)				

BIOLOGICAL ACTIVITY

The $S1P_1$/Edg1, $S1P_3$/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6 or $S1P_5$ /Edg8 activity of the compounds of the present invention can be evaluated using the following assays:

Ligand Binding to Edg/S1P Receptors Assay

^{33}P-sphingosine-1-phosphate was synthesized enzymatically from γ^{33}P-ATP and sphingosine using a crude yeast extract with sphingosine kinase activity in a reaction mix containing 50 mM KH_2PO_4, 1 mM mercaptoethanol, 1 mM Na_3VO_4, 25 mM KF, 2 mM semicarbazide, 1 mM Na_2EDTA, 5 mM $MgCl_2$, 50 mM sphingosine, 0.1% TritonX-114, and 1 mCi γ^{33}P-ATP (NEN; specific activity 3000 Ci/mmol). Reaction products were extracted with butanol and ^{33}P-sphingosine-1-phosphate was purified by HPLC.

Cells expressing EDG/S1P receptors were harvested with enzyme-free dissociation solution (Specialty Media, Lavallette, NJ). They were washed once in cold PBS and suspended in binding assay buffer consisting of 50 mM HEPES-Na, pH 7.5, 5mM $MgCl_2$, 1mM $CaCl_2$, and 0.5% fatty acid-free BSA. ^{33}P-sphingosine-1-phosphate was sonicated with 0.1 nM sphingosine-1-phosphate in binding assay buffer; 100 µl of the ligand mixture was added to 100 µl cells (1 x 10^6 cells/ml) in a 96 well microtiter dish. Binding was performed for 60 min at room temperature with gentle mixing. Cells were then collected onto GF/B filter plates with a Packard Filtermate Universal Harvester. After drying the filter plates for 30 min, 40 µl of Microscint 20 was added to each well and binding was measured on a Wallac Microbeta Scintillation Counter. Non-specific binding was defined as the amount of radioactivity remaining in the presence of 0.5 µM cold sphingosine-1-phosphate.

Alternatively, ligand binding assays were performed on membranes prepared from cells expressing Edg/S1P receptors. Cells were harvested with enzyme-free dissociation solution and washed once in cold PBS. Cells were disrupted by homogenization in ice cold 20 mM HEPES pH 7.4, 10 mM EDTA using a Kinematica polytron (setting 5, for 10 seconds). Homogenates were centrifuged at 48,000 x g for 15 min at 4°C and the pellet was suspended in 20 mM HEPES pH 7.4, 0.1 mM EDTA. Following a second centrifugation, the final pellet was suspended in 20 mM HEPES pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$. Ligand binding assays were performed as described above, using 0.5 to 2 µg of membrane protein.

Agonists and antagonists of Edg/S1P receptors can be identified in the ^{33}P-sphingosine-1-phosphate binding assay. Compounds diluted in DMSO, methanol, or other solvent, were mixed with probe containing ^{33}P-sphingosine-1-phosphate and binding assay buffer in microtiter dishes. Membranes prepared from

cells expressing Edg/S1P receptors were added, and binding to ^{33}P-sphingosine-1-phosphate was performed as described. Determination of the amount of binding in the presence of varying concentrations of compound and analysis of the data by non-linear regression software such as MRLCalc (Merck Research Laboratories) or PRISM (GraphPad Software) was used to measure the affinity of compounds for the receptor. Selectivity of compounds for Edg/S1P receptors was determined by measuring the level of ^{33}P-sphingosine-1-phosphate binding in the presence of the compound using membranes prepared from cells transfected with each respective receptor ($S1P_1$/Edg1, $S1P_3$/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6, $S1P_5$/Edg8).

^{35}S-GTPγS Binding Assay

Functional coupling of S1P/Edg receptors to G proteins was measured in a ^{35}S-GTPγS binding assay. Membranes prepared as described in the Ligand Binding to Edg/S1P Receptors Assay (1-10 μg of membrane protein) were incubated in a 200 μl volume containing 20 mM HEPES pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$, 5 μM GDP, 0.1% fatty acid-free BSA (Sigma, catalog A8806), various concentrations of sphingosine-1-phosphate, and 125 pM ^{35}S-GTPγS (NEN; specific activity 1250 Ci/mmol) in 96 well microtiter dishes. Binding was performed for 1 hour at room temperature with gentle mixing, and terminated by harvesting the membranes onto GF/B filter plates with a Packard Filtermate Universal Harvester. After drying the filter plates for 30 min, 40 μl of Microscint 20 was added to each well and binding was measured on a Wallac Microbeta Scintillation Counter.

Agonists and antagonists of S1P/Edg receptors can be discriminated in the ^{35}S-GTPγS binding assay. Compounds diluted in DMSO, methanol, or other solvent, were added to microtiter dishes to provide final assay concentrations of 0.01 nM to 10 μM. Membranes prepared from cells expressing S1P/Edg receptors were added, and binding to ^{35}S-GTPγS was performed as described. When assayed in the absence of the natural ligand or other known agonist, compounds that stimulate ^{35}S-GTPγS binding above the endogenous level were considered agonists, while compounds that inhibit the endogenous level of ^{35}S-GTPγS binding were considered inverse agonists. Antagonists were detected in a ^{35}S-GTPγS binding assay in the presence of a sub-maximal level of natural ligand or known S1P/Edg receptor agonist,

where the compounds reduced the level of ^{35}S-GTPγS binding. Determination of the amount of binding in the presence of varying concentrations of compound was used to measure the potency of compounds as agonists, inverse agonists, or antagonists of S1P/Edg receptors. To evaluate agonists, percent stimulation over basal was calculated as binding in the presence of compound divided by binding in the absence of ligand, multiplied by 100. Dose response curves were plotted using a non-linear regression curve fitting program MRLCalc (Merck Research Laboratories), and EC_{50} values were defined to be the concentration of agonist required to give 50% of its own maximal stimulation. Selectivity of compounds for S1P/Edg receptors was determined by measuring the level of ^{35}S-GTPγS binding in the presence of compound using membranes prepared from cells transfected with each respective receptor.

Intracellular Calcium Flux Assay

Functional coupling of S1P/Edg receptors to G protein associated intracellular calcium mobilization was measured using FLIPR (Fluorescence Imaging Plate Reader, Molecular Devices). Cells expressing S1P/Edg receptors were harvested and washed once with assay buffer (Hanks Buffered Saline Solution (BRL) containing 20mM HEPES, 0.1% BSA and 710 μg/ml probenicid (Sigma)). Cells were labeled in the same buffer containing 500 nM of the calcium sensitive dye Fluo-4 (Molecular Probes) for 1 hour at 37°C and 5% CO_2. The cells were washed twice with buffer before plating $1.5x10^5$ per well (90μl) in 96 well polylysine coated black microtiter dishes. A 96-well ligand plate was prepared by diluting sphingosine-1-phosphate or other agonists into 200 μl of assay buffer to give a concentration that was 2-fold the final test concentration. The ligand plate and the cell plate were loaded into the FLIPR instrument for analysis. Plates were equilibrated to 37°C. The assay was initiated by transferring an equal volume of ligand to the cell plate and the calcium flux was recorded over a 3 min interval. Cellular response was quantitated as area (sum) or maximal peak height (max). Agonists were evaluated in the absence of natural ligand by dilution of compounds into the appropriate solvent and transfer to the Fluo-4 labeled cells. Antagonists were evaluated by pretreating Fluo-4 labeled cells with varying concentrations of compounds for 15 min prior to the initiation of calcium flux by addition of the natural ligand or other S1P/Edg receptor agonist.

Preparation of Cells Expressing S1P/Edg Receptors

Any of a variety of procedures may be used to clone $S1P_1$/Edg1, $S1P_3$/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6 or $S1P_5$/Edg8. These methods include, but are not limited to, (1) a RACE PCR cloning technique (Frohman, et al., 1988, *Proc. Natl. Acad. Sci. USA* 85: 8998-9002). 5′ and/or 3′ RACE may be performed to generate a full-length cDNA sequence; (2) direct functional expression of the Edg/S1P cDNA following the construction of an S1P/Edg-containing cDNA library in an appropriate expression vector system; (3) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a labeled degenerate oligonucleotide probe designed from the amino acid sequence of the S1P/Edg protein; (4) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a partial cDNA encoding the S1P/Edg protein. This partial cDNA is obtained by the specific PCR amplification of S1P/Edg DNA fragments through the design of degenerate oligonucleotide primers from the amino acid sequence known for other proteins which are related to the S1P/Edg protein; (5) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a partial cDNA or oligonucleotide with homology to a mammalian S1P/Edg protein. This strategy may also involve using gene-specific oligonucleotide primers for PCR amplification of S1P/Edg cDNA; or (6) designing 5′ and 3′ gene specific oligonucleotides using the S1P/Edg nucleotide sequence as a template so that either the full-length cDNA may be generated by known RACE techniques, or a portion of the coding region may be generated by these same known RACE techniques to generate and isolate a portion of the coding region to use as a probe to screen one of numerous types of cDNA and/or genomic libraries in order to isolate a full-length version of the nucleotide sequence encoding S1P/Edg.

It is readily apparent to those skilled in the art that other types of libraries, as well as libraries constructed from other cell types-or species types, may be useful for isolating an S1P/Edg-encoding DNA or an S1P/Edg homologue. Other types of libraries include, but are not limited to, cDNA libraries derived from other cells.

It is readily apparent to those skilled in the art that suitable cDNA libraries may be prepared from cells or cell lines which have S1P/Edg activity. The

selection of cells or cell lines for use in preparing a cDNA library to isolate a cDNA encoding S1P/Edg may be done by first measuring cell-associated S1P/Edg activity using any known assay available for such a purpose.

Preparation of cDNA libraries can be performed by standard techniques well known in the art. Well known cDNA library construction techniques can be found for example, in Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Complementary DNA libraries may also be obtained from numerous commercial sources, including but not limited to Clontech Laboratories, Inc. and Stratagene.

An expression vector containing DNA encoding an S1P/Edg-like protein may be used for expression of S1P/Edg in a recombinant host cell. Such recombinant host cells can be cultured under suitable conditions to produce S1P/Edg or a biologically equivalent form. Expression vectors may include, but are not limited to, cloning vectors, modified cloning vectors, specifically designed plasmids or viruses. Commercially available mammalian expression vectors may be suitable for recombinant S1P/Edg expression.

Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to, bacteria such as *E. coli*, fungal cells such as yeast, mammalian cells including, but not limited to, cell lines of bovine, porcine, monkey and rodent origin; and insect cells including but not limited to *Drosophila* and silkworm derived cell lines.

The nucleotide sequences for the various S1P/Edg receptors are known in the art. See, for example, the following:

S1P$_1$/Edg1 Human

Hla, T. and T. Maciag 1990 An abundant transcript induced in differentiating human endothelial cells encodes a polypeptide with structural similarities to G-protein coupled receptors. J. Biol Chem. 265:9308-9313, hereby incorporated by reference in its entirety.

WO91/15583, published on October 17, 1991, hereby incorporated by reference in its entirety.

WO99/46277, published on September 16, 1999, hereby incorporated by reference in its entirety.

S1P1/Edg1 Mouse

WO0059529, published October 12, 2000, hereby incorporated by reference in its entirety.

U.S. No. 6,323,333, granted November 27, 2001, hereby incorporated by reference in its entirety.

S1P1/Edg1 Rat

Lado, D.C., C. S. Browe, A.A. Gaskin, J. M. Borden, and A. J. MacLennan. 1994 Cloning of the rat edg-1 immediate-early gene: expression pattern suggests diverse functions. Gene 149: 331-336, hereby incorporated by reference in its entirety.

U.S. No. 5,585,476, granted December 17, 1996, hereby incorporated by reference in its entirety.

U.S. No. 5856,443, granted January 5, 1999, hereby incorporated by reference in its entirety.

S1P3/Edg3 Human

An, S., T. Bleu, W. Huang, O.G. Hallmark, S. R. Coughlin, E.J. Goetzl 1997 Identification of cDNAs encoding two G protein-coupled receptors for lysosphingolipids FEBS Lett. 417:279-282, hereby incorporated by reference in its entirety.

WO 99/60019, published November 25, 1999, hereby incorporated by reference in its entirety.

U.S. No. 6,130,067, granted October 10, 2000, hereby incorporated by reference in its entirety.

S1P3/Edg3 Mouse

WO 01/11022, published February 15, 2001, hereby incorporated by reference in its entirety.

S1P3/Edg3 Rat

WO 01/27137, published April 19, 2001, hereby incorporated by reference in its entirety.

S1P2/Edg5 Human

An, S., Y. Zheng, T. Bleu 2000 Sphingosine 1-Phosphate-induced cell proliferation, survival, and related signaling events mediated by G Protein-coupled receptors Edg3 and Edg5. J. Biol. Chem 275: 288-296, hereby incorporated by reference in its entirety.

WO 99/35259, published July 15, 1999, hereby incorporated by reference in its entirety.

WO99/54351, published October 28, 1999, hereby incorporated by reference in its entirety.

WO 00/56135, published September 28, 2000, hereby incorporated by reference in its entirety.

S1P2/Edg5 Mouse

WO 00/60056, published October 12, 2000, hereby incorporated by reference in its entirety.

S1P2/Edg5 Rat

Okazaki, H., N. Ishizaka, T. Sakurai, K. Kurokawa, K. Goto, M. Kumada, Y. Takuwa 1993 Molecular cloning of a novel putative G protein-coupled receptor expressed in the cardiovascular system. Biochem. Biophys. Res. Comm. 190:1104-1109, hereby incorporated by reference in its entirety.

MacLennan, A.J., C. S. Browe, A.A. Gaskin, D.C. Lado, G. Shaw 1994 Cloning and characterization of a putative G-protein coupled receptor potentially involved in development. Mol. Cell. Neurosci. 5: 201-209, hereby incorporated by reference in its entirety.

U.S. No. 5,585,476, granted December 17, 1996, hereby incorporated by reference in its entirety.

U.S. No. 5856,443, granted January 5, 1999, hereby incorporated by reference in its entirety.

S1P4/Edg6 Human

Graler, M.H., G. Bernhardt, M. Lipp 1998 EDG6, a novel G-protein-coupled receptor related to receptors for bioactive lysophospholipids, is specifically expressed in lymphoid tissue. Genomics 53: 164-169, hereby incorporated by reference in its entirety.

WO 98/48016, published October 29, 1998, hereby incorporated by reference in its entirety.

U.S. No. 5,912,144, granted June 15, 1999, hereby incorporated by reference in its entirety.

WO 98/50549, published November 12, 1998, hereby incorporated by reference in its entirety.

U.S. No. 6,060,272, granted May 9, 2000, hereby incorporated by reference in its entirety.

WO 99/35106, published July 15, 1999, hereby incorporated by reference in its entirety.

WO 00/15784, published March 23, 2000, hereby incorporated by reference in its entirety.

WO 00/14233, published March 16, 2000, hereby incorporated by reference in its entirety.

S1P4/Edg6 Mouse

WO 00/15784, published March 23, 2000, hereby incorporated by reference in its entirety.

S1P5/Edg8 Human

Im, D.-S., J. Clemens, T.L. Macdonald, K.R. Lynch 2001 Characterization of the human and mouse sphingosine 1-phosphate receptor, S1P5 (Edg-8): Structure-Activity relationship of sphingosine 1-phosphate receptors. Biochemistry 40:14053-14060, hereby incorporated by reference in its entirety.

WO 00/11166, published March 2, 2000, hereby incorporated by reference in its entirety.

WO 00/31258, published June 2, 2000, hereby incorporated by reference in its entirety.

WO 01/04139, published January 18, 2001, hereby incorporated by reference in its entirety.

EP 1 090 925, published April 11, 2001, hereby incorporated by reference in its entirety.

S1P5/Edg8 Rat

Im, D.-S., C.E. Heise, N. Ancellin, B. F. O'Dowd, G.-J. Shei, R. P. Heavens, M. R. Rigby, T. Hla, S. Mandala, G. McAllister, S.R. George, K.R. Lynch 2000 Characterization of a novel sphingosine 1-phosphate receptor, Edg-8. J. Biol. Chem. 275: 14281-14286, hereby incorporated by reference in its entirety.

WO 01/05829, published January 25, 2001, hereby incorporated by reference in its entirety.

Measurement of cardiovascular effects

The effects of compounds of the present invention on cardiovascular parameters can be evaluated by the following procedure:

Adult male rats (approx. 350 g body weight) were instrumented with femoral arterial and venous catheters for measurement of arterial pressure and intravenous compound administration, respectively. Animals were anesthetized with Nembutal (55 mg/kg, ip). Blood pressure and heart rate were recorded on the Gould Po-Ne-Mah data acquisition system. Heart rate was derived from the arterial pulse wave. Following an acclimation period, a baseline reading was taken (approximately 20 minutes) and the data averaged. Compound was administered intravenously (either bolus injection of approximately 5 seconds or infusion of 15 minutes duration), and data were recorded every 1 minute for 60 minutes post compound administration. Data are calculated as either the peak change in heart rate or mean arterial pressure or are calculated as the area under the curve for changes in heart rate or blood pressure versus time. Data are expressed as mean ± SEM. A one-tailed Student's paired t-test is used for statistical comparison to baseline values and considered significant at $p<0.05$.

The S1P effects on the rat cardiovascular system are described in Sugiyama, A., N.N. Aye, Y. Yatomi, Y. Ozaki, K. Hashimoto 2000 Effects of Sphingosine-1-Phosphate, a naturally occurring biologically active lysophospholipid, on the rat cardiovascular system. Jpn. J. Pharmacol. 82: 338-342, hereby incorporated by reference in its entirety.

Measurement of Mouse Acute Toxicity

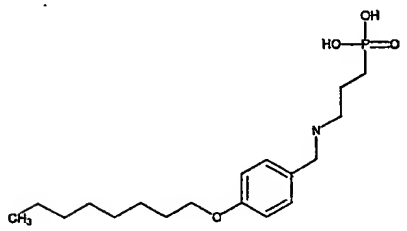
A single mouse is dosed intravenously (tail vein) with 0.1 ml of test compound dissolved in a non-toxic vehicle and is observed for signs of toxicity. Severe signs may include death, seizure, paralysis or unconciousness. Milder signs are also noted and may include ataxia, labored breathing, ruffling or reduced activity relative to normal. Upon noting signs, the dosing solution is diluted in the same vehicle. The diluted dose is administered in the same fashion to a second mouse and is likewise observed for signs. The process is repeated until a dose is reached that produces no signs. This is considered the estimated no-effect level. An additional mouse is dosed at this level to confirm the absence of signs.

Assessment of Lymphopenia

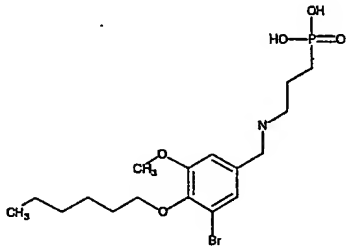
Compounds are administered as described in Measurement of Mouse Acute Toxicity and lymphopenia is assessed in mice at three hours post dose as follows. After rendering a mouse unconscious by CO_2 to effect, the chest is opened, 0.5 ml of blood is withdrawn via direct cardiac puncture, blood is immediately stabilized with EDTA and hematology is evaluated using a clinical hematology autoanalyzer calibrated for performing murine differential counts (H2000, CARESIDE, Culver City CA). Reduction in lymphocytes by test treatment is established by comparison of hematological parameters of three mice versus three vehicle treated mice. The dose used for this evaluation is determined by tolerability using a modification of the dilution method above. For this purpose, no-effect is desirable, mild effects are acceptable and severely toxic doses are serially diluted to levels that produce only mild effects.

Example of Non-selective and Selective S1P1/Edg1 Agonists

To illustrate the utility of selective S1P1/Edg1 agonists, the activity of 2 compounds in GTPgS binding assays using human S1P1/Edg1 and S1P3/Edg3 receptors and mouse acute toxicity and lymphopenia assays conducted as described above are shown. Example 2 is a non-selective potent agonist of S1P1/Edg1 and S1P3/Edg3 that is highly toxic to mice at doses greater than 0.1 mg/kg, and induces immunosuppression as measured by lymphopenia at 0.1 mg/kg. Example 77 is a selective agonist of S1P1/Edg1 that induces lymphopenia at 10 mg/kg without apparent toxicity.



EXAMPLE 2



EXAMPLE 77

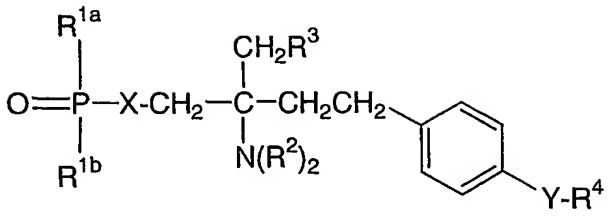
Compound	$S1P_1$ EC_{50} (nM)	$S1P_3$ EC_{50} (nM)	IV dose (mg/kg)	Toxicity	Lymphocytes*
Example 2	1.5	6.0	3	Lethal	NE**
			0.25	severe	NE
			0.1	mild to severe	65
Example 77	8.4	>10000	4	none	38

* % reduction

** NE = not evaluable

A further embodiment of the invention encompasses a method of identifying a candidate compound which is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor, wherein said candidate compound possesses a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said candidate compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the candidate compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl,

comprising:

(1) providing a first receptor preparation comprising:
(a) a recombinant cell expressing the $S1P_1$/Edg1 receptor or a functional equivalent of the $S1P_1$/Edg1 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
(b) a membrane preparation of a recombinant cell in accordance with subsection (1)(a);

(2) providing a second receptor preparation comprising:
(a) a recombinant cell expressing the $S1P_3$/Edg3 receptor or a functional equivalent of the $S1P_3$/Edg3 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
(b) a membrane preparation of a recombinant cell in accordance with subsection (2)(a);

(3) separately contacting said cells or membrane preparations with the candidate compound; and

(4) determining whether the candidate compound binds to and activates the $S1P_1$/Edg1 and $S1P_3$/Edg3 receptors by measuring the level of a signal generated from the interaction of the candidate compound with each receptor, thereby indicating whether the candidate compound is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor.

For purposes of this Specification, any pathway that is activated by the $S1P_1$/Edg1 and/or $S1P_3$/Edg3 receptors upon contact with an agonist can result in a detectable signal indicating that the receptor has been activated. Activation of the receptor by an agonist, for example, can be identified by an increase in the concentration of a relevant second messenger influenced by the receptor within cells expressing the receptor (an increase that would not be observed in cells not contacted by a receptor agonist). Those of skill in the art can readily identify an assay suitable for detecting an increase in the level of an intracellular second messenger or a

detectable extracellular signal indicative of receptor activation. The signal's primary purpose is to detect (either directly or indirectly) the activation and signaling of the receptor. The signal can be either a component of the pathway or responsive to the presence or functioning of a component of the pathway. In accordance with this description, therefore, the signal can be responsive to an intracellular event which is part of the biochemical cascade initiated by receptor activation or responsive to an extracellular event such as pH changes that occur upon receptor activation. The signal can, thus, be detected by outward characteristics or by a molecule present within or administered to the cells that responds to the signal. One class of molecules that respond to intracellular changes includes those that act on changes in calcium concentration (*e.g.*, aequorin (a jellyfish protein)) which acts on the substrate coelenterazine. Other molecules in that class include calcium chelators with fluorescence capabilities, such as FURA-2, indo-1, Fluo-3, and Fluo-4 The level of cAMP is another signal that is measured. This can be measured, for instance, byradio-immuno or protein binding assays (*e.g.*, using Flashplates or a scintillation proximity assay). The changes in cAMP can also be determining by measuring the activity of the enzyme, adenylyl cyclase. cAMP assays are described in the art, *see, e.g.*, Jakajima *et al.*, 1992 *J. Biol. Chem.* 247:2437-2442; Tigyi *et al.*, 1996 *J. Neurochem.* 66:549-558. Alternative assays disclosed in the art measure changes in inositol 1,4,5-triphosphate levels (*see, e.g.*, Tigyi *et al.*, 1996 *J. Neurochem.* 66:537-548); Cl^- ion efflux (*see, e.g.*, Postma *et al.*, 1996 *EMBO J.* 15:63-72; and Watsky, 1995 *Am. J. Physiol.* 269:C1385-C1393); or, as provided in examples above, changes in intracellular Ca2+ levels (*see also*, Tigyi *et al.*, 1996 *J. Neurochem.* 66:537-548. In the illustrated examples of the instant invention, binding of ^{35}S-GTPγS to G proteins coupled to receptors is detected. This has been described in the art in the following references:

Milligan, 1988, Journal 255:1-13
Stanton and Beer, 1997, Journal 320:267-275

It is appreciated by those skilled in the art that the dose of the candidate compound contacted to said cells or membranes expressing each receptor will affect the signal generated in the assay. A positive and greater signal at the S1P1/Edg1 receptor over the S1P3/Edg3 receptor at an equivalent dose will indicate a compound

that is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor. An "equivalent dose" means a substantially equal amount of the compounds and is well understood by artisans skilled in the art. However, the present invention is meant to include identifying the compounds using any dose as long as one skilled in the art is determining whether the candidate compounds are agonists of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor.

For purposes of this Specification, the following terms have the indicated meanings:

"S1P" means sphingosine 1-phosphate.

"Functional equivalents" are defined herein as receptors which may not possess the exact amino acid sequence due to alternative splicing, deletions, mutations, or additions, but retain the biological activity of the $S1P_1$/Edg1 or $S1P_3$/Edg3 receptor (*e.g.*, binding of sphingosine 1-phosphate and transduction of signals through Gi, Gq, or $G_{12/13}$ heterotrimeric G proteins). Minor changes in the sequence are known in the art not to change the functionality of the receptors. See for example the following, which are hereby incorporated by reference in their entirety:

Truncation of C-terminus of Edg1:

(Liu et al., 1999, Journal 10:1179-90.)

(Watterson et al., 2002, Journal 277:5767-5777.)

Site Directed Mutagenesis of Edg1

(Parrill et al., 2000, Journal 275:39379-84.)

An embodiment of the invention encompasses the method of the present invention wherein the method further comprises conducting the method in the presence of labeled or unlabeled S1P, di-hydro S1P or a ligand for the S1P1/Edg1 and/or S1P3/Edg3 receptor; provided that if a ligand is utilized that is specific for either the S1P1/Edg1 or S1P3/Edg3 receptor, the receptor ligand utilized in the first receptor preparation is a ligand of the S1P1/Edg1 receptor and the ligand utilized in

the second receptor preparation is a ligand of the S1P3/Edg3 receptor; and provided, further, that the method would additionally comprise measuring the level of a signal generated from the interaction of the S1P, di-hydro S1P or ligand; wherein a compound that effects a reduction of the signal from the interaction of the S1P, di-hydro S1P or ligand, with the receptor and activates the S1P1/Edg1 receptor at a greater level than that obtained at the S1P3/Edg3 receptor is a selective agonist of the S1P1/Edg1 receptor.

Another embodiment of the invention encompasses the method of the present invention wherein the signal indicates extracellular pH changes caused by receptor activation.

Another embodiment of the invention encompasses the method of the present invention wherein the signal indicates levels of cAMP present within the cell.

Another embodiment of the invention encompasses the method of the present invention wherein the signal indicates adenylate cyclase accumulation.

Another embodiment of the invention encompasses the method of the present invention wherein the signal indicates Ca+ flux.

Another embodiment of the invention encompasses the method of the present invention wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the method of the present invention wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the method of the present invention wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the method of the present invention wherein the candidate compound has a selectivity for the

$S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the method of the present invention wherein the candidate compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

The invention further encompasses a method of identifying a candidate compound which is an agonist of the $S1P_1$/Edg1 receptor that is selective over the S1P3/Edg3 receptor, wherein said candidate compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said candidate compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay, comprising:

(1) providing a first receptor preparation comprising:
   (a) a recombinant cell expressing the S1P1/Edg1 receptor or a functional equivalent of the S1P1/Edg1 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
   (b) a membrane preparation of a recombinant cell in accordance with subsection (1)(a);

(2) providing a second receptor preparation comprising:
   (a) a recombinant cell expressing the S1P3/Edg3 receptor or a functional equivalent of the S1P3/Edg3 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
   (b) a membrane preparation of a recombinant cell in accordance with subsection (2)(a);

(3) separately contacting said cells or membrane preparations with the candidate compound; and

(4) determining whether the candidate compound binds to and activates the $S1P_1$/Edg1 and $S1P_3$/Edg3 receptors by measuring the level of a signal generated from the interaction of the candidate compound with each receptor, thereby indicating whether the candidate compound is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor.

Within this embodiment is encompassed the above method wherein the method further comprises conducting the method in the presence of labeled or unlabeled S1P, di-hydro S1P or a ligand for the S1P1/Edg1 and/or S1P3/Edg3 receptor; provided that if a ligand is utilized that is specific for either the S1P1/Edg1 or S1P3/Edg3 receptor, the receptor ligand utilized in the first receptor preparation is a ligand of the S1P1/Edg1 receptor and the ligand utilized in the second receptor preparation is a ligand of the S1P3/Edg 3 receptor; and provided, further, that the method would additionally comprise measuring the level of a signal generated from the interaction of the S1P, di-hydro S1P or ligand; wherein a compound that effects a reduction of the signal from the interaction of the S1P, di-hydro S1P or ligand, with the receptor and activates the SIP1/Edg1 receptor at a greater level than that obtained at the S1P3/Edg3 receptor is a selective agonist of the SIP1/Edg1 receptor.

Also within this embodiment is encompassed the above method wherein the signal indicates extracellular pH changes caused by receptor activation.

Also within this embodiment is encompassed the above method wherein the signal indicates levels of cAMP present within the cell.

Also within this embodiment is encompassed the above method wherein the signal indicates adenylate cyclase accumulation.

Also within this embodiment is encompassed the above method wherein the signal indicates Ca+ flux.

Also within this embodiment is encompassed the above method wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the

$S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1PR_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

REFERENCES:

Liu, C.H., S. Thangada, M.J. Lee, J.R. Van Briocklyn, S. Spiegel, and T. Hla. 1999. Ligand-induced trafficking of the sphingosine-1-phosphate receptor EDG1. *Mol. Biol. Cell.* 10:1179-90.

Milligan, G. 1988. Techniques used in the identification and analysis of function of pertussis toxin-sensitive guanine nucleotide binding proteins. *Biochem. J.* 255:1-13.

Parrill, A.L., D. Wang, D.L. Bautista, J.R. Van. Brocklyn, Z. Lorincz, D.J. Fischer, D.L. Baker, K. Liliom, S. Spiegel, and G. Tigyi. 2000. Identification of Edg1 receptor residues that recognize sphingosine 1. phosphate. *J. Biol. Chem.* 275:39379-84.

Stanton, J.A., and M.S. Beer. 1997. Characterisation of a cloned human 5-HT_{1A} receptor cell line using [^{35}S]GTPγS binding. *Euro. J. Pharm.* 320:267-275.

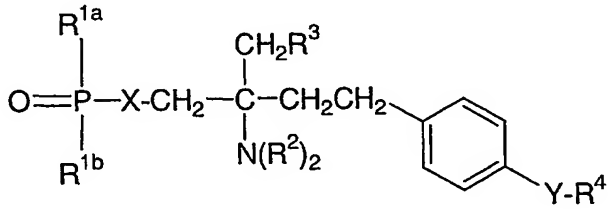
Watterson, K.R., E. Johnston, C. Chalmers, A. Pronin, S.J. Cook, J.L. Benovic, and T.M. Palmer. 2002. Dual regulation of EDG1/S1P1 receptor phosphorylation

and internalization by protein kinase C and G-protein-coupled receptor kinase 2. *J. Biol. Chem.* 277:5767-5777.

RESPIRATORY DISEASES

An embodiment of the invention encompasses a method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

Within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

The invention also encompasses a method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

Within this embodiment is encompassed the above method wherein the compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the

$S1P_1$/Edg1 receptor to the EC_{50} for the S1PR3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

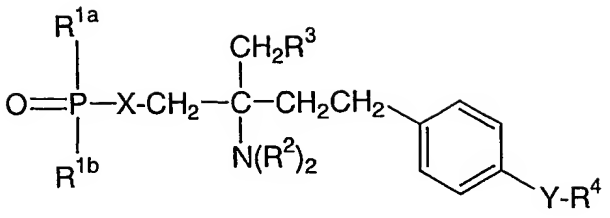
Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1PR3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

The invention also encompasses any of the above embodiments wherein the respiratory disease or condition is selected from the group consisting of: asthma, chronic bronchitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, infant respiratory distress syndrome, cough, eosinophilic granuloma, respiratory syncytial virus bronchiolitis, bronchiectasis, idiopathic pulmonary fibrosis, acute lung injury and bronchiolitis obliterans organizing pneumonia.

Another embodiment of the invention encompasses any of the above embodiments further comprising concomitantly or sequentially administering one or more agents selected from the group consisting of: a Leukotriene receptor antagonist, a Leukotriene biosynthesis inhibitor, an M2/M3 antagonist, phosphodiesterase 4 inhibitor, calcium activated chloride channel 1 agonist, a corticosteroid, an H1 receptor antagonist, a beta 2 adrenoreceptor agonist and a prostaglandin D2 antagonist. These compounds are well known in the art.

The invention also encompasses a method of modulating airway function in a mammalian patient in need thereof comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for modulating airway function, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

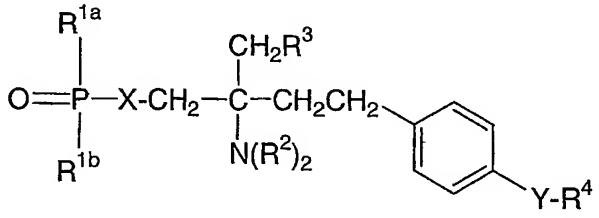
R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

The invention also encompasses a method of reducing or preventing the activation of the S1P1/Edg1 receptor in a mammalian patient in need thereof comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for reducing or preventing the activation of S1P1/EDG1 receptor, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

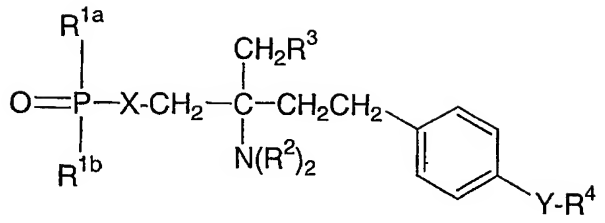
R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

The invention also encompasses a method of inhibiting an infiltration of a lymphocyte into a respiratory tissue in a mammalian patient in need thereof by promoting a sequestration of the lymphocyte in a lymph node thereby preventing release of a pro-inflammatory mediator in the respiratory tissue comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for modulating airway function, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

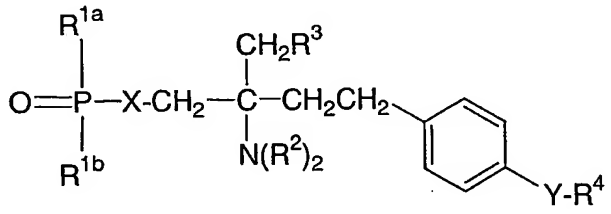
Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

WHAT IS CLAIMED IS:

1. A method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

2. The method according to Claim 1 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

3. The method according to Claim 2 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

4. The method according to Claim 3 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

5. The method according to Claim 4 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 2000

fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

6. A method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

7. The method according to Claim 6 wherein the compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

8. The method according to Claim 6 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

9. The method according to Claim 8 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

10. The method according to Claim 9 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1PR_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

11. The method according to Claim 10 wherein the compound has a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

12. The method according to Claim 1 wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease selected from the group consisting of: systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

13. The method according to Claim 1 wherein the immunoregulatory abnormality is bone marrow or organ transplant rejection or graft-versus-host disease.

14. The method according to Claim 1 wherein the immunoregulatory abnormality is selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies,

reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, chronic lymphocytic leukemia, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic

failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

15. The method according to Claim 1 wherein the immunoregulatory abnormality is multiple sclerosis.

16. The method according to Claim 1 wherein the immunoregulatory abnormality is rheumatoid arthritis.

17. The method according to Claim 1 wherein the immunoregulatory abnormality is systemic lupus erythematosus.

18. The method according to Claim 1 wherein the immunoregulatory abnormality is psoriasis.

19. The method according to Claim 1 wherein the immunoregulatory abnormality is rejection of transplanted organ or tissue.

20. The method according to Claim 1 wherein the immunoregulatory abnormality is inflammatory bowel disease.

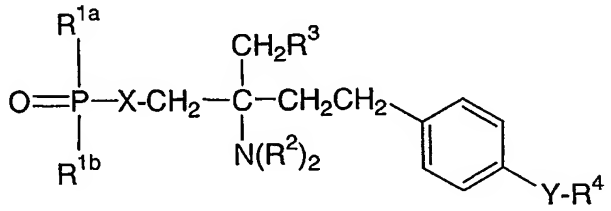
21. The method according to Claim 1 wherein the immunoregulatory abnormality is a malignancy of lymphoid origin.

22. The method according to Claim 21 wherein the immunoregulatory abnormality is acute and chronic lymphocytic leukemias and lymphomas.

23. A pharmaceutical composition comprised of a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating an immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by

the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: -CH_2-, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

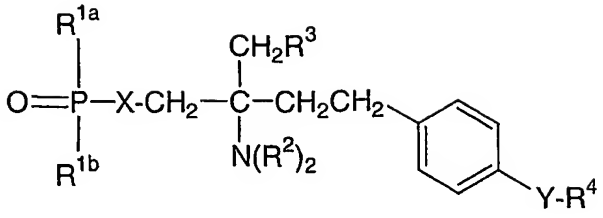
R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl,

in combination with a pharmaceutically acceptable carrier.

24. A pharmaceutical composition comprised of a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating an immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay, in combination with a pharmaceutically acceptable carrier.

25. A method of identifying a candidate compound which is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor, wherein said candidate compound possesses a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said candidate compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the candidate compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl,

comprising:

(1) providing a first receptor preparation comprising:
(a) a recombinant cell expressing the $S1P_1$/Edg1 receptor or a functional equivalent of the $S1P_1$/Edg1 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
(b) a membrane preparation of a recombinant cell in accordance with subsection (1)(a);

(2) providing a second receptor preparation comprising:
(a) a recombinant cell expressing the $S1P_3$/Edg3 receptor or a functional equivalent of the $S1P_3$/Edg3 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
(b) a membrane preparation of a recombinant cell in accordance with subsection (2)(a);

(3) separately contacting said cells or membrane preparations with the candidate compound; and

(4) determining whether the candidate compound binds to and activates the $S1P_1$/Edg1 and $S1P_3$/Ed3 receptors by measuring the level of a signal generated from the interaction of the candidate compound with each receptor, thereby indicating whether the candidate compound is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor.

26. A method in accordance with claim 25 wherein the method further comprises conducting the method in the presence of labeled or unlabeled S1P, di-hydro S1P or a ligand for the S1P1/Edg1 and/or S1P3/Edg3 receptor; provided that if a ligand is utilized that is specific for either the S1P1/Edg1 or S1P3/Edg3 receptor, the receptor ligand utilized in the first receptor preparation is a ligand of the S1P1/Edg1 receptor and the ligand utilized in the second receptor preparation is a ligand of the S1P3/Edg3 receptor; and provided, further, that the method would additionally comprise measuring the level of a signal generated from the interaction of the S1P, di-

hydro S1P or ligand; wherein a compound that effects a reduction of the signal from the interaction of the S1P, di-hydro S1P or ligand, with the receptor and activates the S1P1/Edg1 receptor at a greater level than that obtained at the S1P3/Edg3 receptor is a selective agonist of the S1P1/Edg1 receptor.

27. A method in accordance with claim 25 wherein the signal indicates extracellular pH changes caused by receptor activation.

28. A method in accordance with claim 25 wherein the signal indicates levels of cAMP present within the cell.

29. A method in accordance with claim 25 wherein the signal indicates adenylate cyclase accumulation.

30. A method in accordance with claim 25 wherein the signal indicates Ca+ flux.

31. The method according to Claim 25 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

32. The method according to Claim 31 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

33. The method according to Claim 32 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

34. The method according to Claim 33 wherein the candidate compound has a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

35. The method according to Claim 25 wherein the candidate compound possesses an EC_{50} for binding to the S1P1/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

36. A method of identifying a candidate compound which is an agonist of the S1P1/Edg1 receptor that is selective over the S1P3/Edg3 receptor, wherein said candidate compound possesses a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said candidate compound possesses an EC_{50} for binding to the S1P1/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay, comprising:

(1) providing a first receptor preparation comprising:
   (a) a recombinant cell expressing the S1P1/Edg1 receptor or a functional equivalent of the S1P1/Edg1 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
   (b) a membrane preparation of a recombinant cell in accordance with subsection (1)(a);

(2) providing a second receptor preparation comprising:
   (a) a recombinant cell expressing the S1P3/Edg3 receptor or a functional equivalent of the S1P3/Edg3 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
   (b) a membrane preparation of a recombinant cell in accordance with subsection (2)(a);

(3) separately contacting said cells or membrane preparations with the candidate compound; and

(4) determining whether the candidate compound binds to and activates the $S1P_1$/Edg1 and $S1P_3$/Ed3 receptors by measuring the level of a signal generated from the interaction of the candidate compound with each receptor, thereby indicating whether the candidate compound is an agonist of the $S1P_1$/Edg1 receptor that is selective over the S1P3/Edg3 receptor.

37. A method in accordance with claim 36 wherein the method further comprises conducting the method in the presence of labeled or unlabeled S1P, di-hydro S1P or a ligand for the S1P1/Edg1 and/or S1P3/Edg3 receptor; provided that if a ligand is utilized that is specific for either the S1P1/Edg1 or S1P3/Edg3 receptor, the receptor ligand utilized in the first receptor preparation is a ligand of the S1P1/Edg1 receptor and the ligand utilized in the second receptor preparation is a ligand of the S1P3/Edg 3 receptor; and provided, further, that the method would additionally comprise measuring the level of a signal generated from the interaction of the S1P, di-hydro S1P or ligand; wherein a compound that effects a reduction of the signal from the interaction of the S1P, di-hydro S1P or ligand, with the receptor and activates the SIP1/Edg1 receptor at a greater level than that obtained at the S1P3/Edg3 receptor is a selective agonist of the SIP1/Edg1 receptor.

38. A method in accordance with claim 36 wherein the signal indicates extracellular pH changes caused by receptor activation.

39. A method in accordance with claim 36 wherein the signal indicates levels of cAMP present within the cell.

40. A method in accordance with claim 36 wherein the signal indicates adenylate cyclase accumulation.

41. A method in accordance with claim 36 wherein the signal indicates Ca+ flux.

42. The method according to Claim 36 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

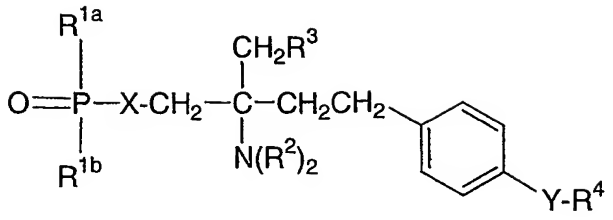
43. The method according to Claim 42 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

44. The method according to Claim 43 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1PR3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

45. The method according to Claim 44 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

46. A method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

47. The method according to Claim 46 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

48. The method according to Claim 47 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

49. The method according to Claim 48 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

50. The method according to Claim 49 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

51. A method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

52. The method according to Claim 51 wherein the compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

53. The method according to Claim 52 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

54. The method according to Claim 53 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

55. The method according to Claim 54 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1PR3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

56. The method according to Claim 55 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1PR3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

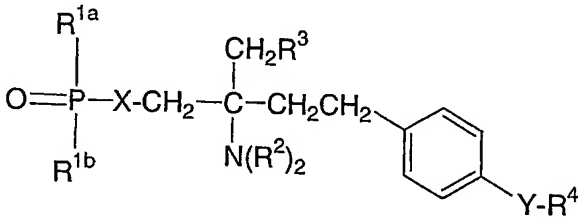
57. The method according to Claim 46 wherein the respiratory disease or condition is selected from the group consisting of: asthma, chronic bronchitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, infant respiratory distress syndrome, cough, eosinophilic granuloma, respiratory syncytial virus bronchiolitis, bronchiectasis, idiopathic pulmonary fibrosis, acute lung injury and bronchiolitis obliterans organizing pneumonia.

58. The method according to Claim 46 further comprising concomitantly or sequentially administering one or more agents selected from the

group consisting of: a Leukotriene receptor antagonist, a Leukotriene biosynthesis inhibitor, an M2/M3 antagonist, phosphodiesterase 4 inhibitor, calcium activated chloride channel 1 agonist, a corticosteroid, an H1 receptor antagonist, a beta 2 adrenoreceptor agonist and a prostaglandin D2 antagonist.

59. A method of modulating airway function in a mammalian patient in need thereof comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for modulating airway function, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

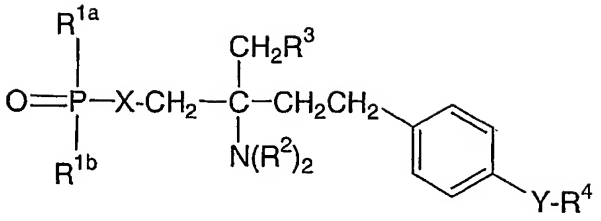
R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

60. A method of reducing or preventing the activation of the S1P1/Edg1 receptor in a mammalian patient in need thereof comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for reducing or preventing the activation of S1P1/Edg1 receptor, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

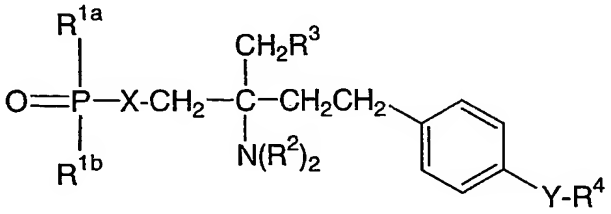
R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

61. A method of inhibiting an infiltration of a lymphocyte into a respiratory tissue in a mammalian patient in need thereof by promoting a sequestration of the lymphocyte in a lymph node thereby preventing release of a pro-inflammatory mediator in the respiratory tissue comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for modulating airway function, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.